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Review

A comprehensive mechanistic basis of prostate cancer advancement & its personalized implementation-bridging the gap: present state and future prospect

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Abstract

Despite significant achievements in prostate cancer mechanistic understanding and its targeted therapies, currently there exists several major challenges that mainly arises during the therapy of advanced prostate cancer. Present prostate cancer precision medicine strategy principally suffers from several practical concerns, particularly in point of therapeutic resistance, tumor heterogeneity, complex clinical & pathological behavior and an extensive genomic perturbation landscape.

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Prostate Cancer Systems-Medicine Initiative is a global trans-disciplinary movement taken from corresponding scientific domains to critically determine the nature of this major existing challenges and its corresponding most possible solutions by systematically accumulating the present existing knowledge. Basically, it explains the importance of broad spectrum cancer hallmark based integrative approaches for development of combination therapy associated strategic measures for metastatic castration resistant prostate cancer. The major findings of this initiative can be summarized by identification of 136 therapeutic resistance mediators, 103 prostate cancer driver oncogenes and 8 progression pathways along with 5 terrain factors which centrally drives the basic events in prostate cancer pathogenesis, its further metastatic propagation and ultimate therapeutic resistance. In addition, it also attempts to summarize the critical features and basic challenging aspects of current therapeutic options.

Keywords
Precision medicine; Therapy resistance; Cancer hallmarks; Terrain factors; Castration resistant prostate cancer (CRPC); Bone metastasis; Androgen receptor (AR)

1. Introduction: prostate cancer systems-medicine initiative

Prostate cancer can be considered as the second leading cause of cancer in men population and is accountable for around one fifth of cancer related death globally. Recent survey indicates an enhancement of its incidence rate in both developed and developing countries including India [1, 2]. Although organ confined prostate cancer is totally curable but in case of aggressive metastatic disease, the scenario is quite frustrating. Despite significant advancement in prostate cancer underlying mechanistic understanding and its numerous therapeutic modalities, currently there is no effective therapy available to completely cure advanced prostate cancer and its related aggressive features like bone metastasis and castration resistance [3–8].

Nearly 80 years of extensive research has been given to decipher the basic molecular mechanisms of prostate cancer development, its aggressive manifestations and ultimate emergence of therapeutic resistance. This enormous efforts has led to the development of present therapeutic strategies for advanced prostate cancer treatment along with a number of FDA approved drugs and many more therapeutic agents with a diverse range of therapeutic activities [3, 5]. But, the major challenge is that till now we don't know how to apply these agents more effectively in which manner to gain the complete remission of CRPC progression [6, 7]. The principal future aim in prostate cancer research demands an effective therapeutic strategy that will sequentially modify and replace present-day therapeutic approaches by integrating knowledge's from several key specific areas and major factors that collectively determines the state of castration resistance and its subsequent bone metastatic progression in advanced prostate cancer patients. Basically, it will follow an individualized systems-medicine strategy that will target the state of the disease in a patient by combining information from patient specific genomic landscape to its underlying molecular mechanisms and pathological status along with the knowledge of available therapeutic agents. It is the principal aim of Prostate Cancer-Systems Medicine Initiative, a global trans-disciplinary movement taken from corresponding scientific domains in order to take a major leading steps for identification & reassessment of existing challenges and for finding necessary strategic measures to cross this formidable barriers in advanced prostate cancer treatment along with its personalized focusing. In this review, we provide a theoretical framework for development of prostate cancer precision medicine strategies from its wide-spectrum mechanistic understanding in association with a critical assessment of its current therapeutic approaches.

2. Methods

In the current study, we have followed an extensive literature searching for identification of potential oncogenes and therapeutic resistance mediators in prostate cancer from the currently available literatures. In this regard, initially we have obtained the basic information from Human Prostate Cancer Hallmarks Map Database [8]. Next, a further detail search was performed based on extracted basic information by following their references and associated particulars. For these purpose, we have used free search engine PubMed for extraction of specific information regarding an oncogene or key driver of therapeutic resistance in the present context. For instance, by using the general keyword 'role of (oncogene, like STAT3) in prostate cancer progression' and more specifically by applying individual keywords 'tumorigenesis', 'cell proliferation', 'cell survival', 'metastasis', 'therapy resistance' and 'castration resistance'. For each of the oncogene, a detail literature searching was performed by following the above manner to identify its most possible involvement in this disease. In addition, in each of the cases literature searching associated cross verification was also done by different researchers. The total extracted information has been listed in the Supplementary files.

3. Current therapeutic approaches in advanced prostate cancer and their limitations

Since early 1940s, from the time of Charles Huggins, the basic treatment procedure for advanced forms of prostate cancer

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TABLE 1. Prostate cancer associated therapeutic resistance profile.

Type of prostate cancer therapeutic resistance	Number of key drivers in corresponding therapeutic resistance	Key mediator of corresponding therapeutic resistance	Reference
Docetaxel Resistance	55	ERG, P38, P53, P21, NF-KB, TLR4, CLU, EZH2, DAB2IP, PI3K, AKT1, ABCB1, SLCO1B3, PTOV1, MTOR, S6K, AXL, HSP27, AR, HSP90, PIAS1, KDM5D, CDC25C, LZTS1, PLK1, CHEK1, SLCO1B3, LIMK1, PAK4, CXCR4, , PIM1, IL-6, TR4, PTHrP, KRAS, EGFR, INSR, IGF1R, TLR4, HMGB1, RAGE, PAR1, LDH, TNFAIP8, CXCR6, MRP4, KIFC1, ELF1, AKAP12, MALAT1, SDC1, CDC20, PrLZ, MRP4, ZEB1, ZEB2	Supplementary File-Sheet_1
Paclitaxel Resistance	28	PLK1, CLIP-170, AR, MCL-1, AURKA, CTNNB1, GSK3B, CK18, TWIST1, YB-1, RSK, CLU, SHH, ESR1, PHB, SKP2, MiR-302a, BCRP, Linc00518, JAG1, NOTCH1, YES1, SOX2, ETS1, PIM-1, SIRT1, BCL2, MSK1	
Enzalutamide Resistance	22	RSK1, YB-1, NF-Kb, CXCR7, ERK, NOTCH1, STAT3, AR, BECN1, AKR1C3, CTNNB1, TGFB1, SNAIL, AR-V7, hnRNPA1, HER2, PKC, TWIST1, AKT1, N-MYC, ATM, SOX2, SYP	
Abiraterone Acetate Resistance	8	AR-V7, AR-V9, AR, HSD3B1, SYP, CDK4, CDK6, PTEN	
Cabazitaxel Resistance	7	ERG, CCR2, CCL2, ABCB1, MiR-181a, SLCO1B3, CLU	
Doxorubicin Resistance	11	TCF3, GADD153, BRCA1, c-MET, PI3K, AKT, TNFAIP8, EGFR, ABCG4, CREB, MTOR	
Radiation Resistance	48	CAV1, COX2, GIPC1, LDH5, DAB2IP, EZH2, AKR1C3, PGF2A, PKC, RAS, RKIP, HIF1A, ASAH1, ACK1, AR, ATM, ATR, BRCA1, BRCA2, IL-6, P22PHOX, GP91PHOX, NOX2, NOX4, ZEB1, PRKCE, SMC1A, CD44, ERBB2, P38, LITAF, MiR-106a, CD105, HULC, BECN1, DAB2IP, PDGF-D, P53, P21, PI3K, AKT, MTOR, ASAH1, GIPC1, AURKA, SOD2, ADAM9, PAK6	

mainly involves androgen ablation or androgen deprivation therapy (ADT) through either by surgical or medical castration [9]. But, that standard line of treatment only provides a temporary relief and majority of patients will eventually acquire resistance to androgen deprivation therapy and after 18 to 36 months, they ultimately progress towards a highly aggressive forms of this disease known as castration resistant prostate cancer (CRPC) [6, 10]. One of the major success of current therapeutics is the improvement of median overall survival which results in reduction of mortality rates among advanced prostate cancer patients [11–17]. This improvement is mostly achieved due to the introduction of new types of therapeutic agents from the grounds of both chemotherapies, radiation therapies and immunotherapies for treatment of metastatic CRPCs [3–6, 16]. But, at the same time there are several critical inconsistencies exists among currently used therapeutics, causing unavoidable therapeutic failure which still maintains the state of lack of proper curative therapy for CRPC. The main drawbacks of currently available therapeutic strategies for treatment of advanced prostate cancer can be summarized as- lack of proper responsiveness among many patients towards these agents, acquisition of significant levels of primary and secondary resistance and development of ultimate cross resistance [10, 12–14, 16, 17]. Here, we will present a critical overviews over these major challenging aspects.

3.1 Challenges in current sequencing strategies for advanced prostate cancer and associated cross resistance

For treatment of CRPC, currently nine drugs are mainly used, out of which, Docetaxel, Enzalutamide, Apalutamide, Darolutamide and Abiraterone are often used as a first line chemotherapy and Sipleucel-T, Radium-223 dichloride, Cabazitaxel and Olaparib are considered as a second line of defense [3, 5, 11–14, 18–20]. For the first line of treatment in CRPC patients, the optimal sequencing between next generation anti-androgen drugs with taxane chemotherapy in point of efficacy and cross-resistance still remains unknown [21–23]. In this context, no chemotherapeutic drug has been identified more superior in performance than other types of available agents as the first line therapy for advanced prostate cancer. Additionally, the specific treatment impacts of prior therapies in the level of clinical response and drug efficacies in prostate cancer remains largely unrecognized [24]. Docetaxel, an anti-mitotic agent was first approved by FDA as chemotherapeutic drug for the first line treatment of CRPC patients with considerable levels of survival benefits [14]. Docetaxel preferentially targets beta tubulin in microtubules and thereby inhibits mitosis through induction of microtubule stabilization [14]. But, unfortunately nearly 50% of patients with metastatic CRPC, do not provide any desirable clinical response to docetaxel based therapy and many patients often produces significant level of resistance [12–14]. For this major reason, currently several next-generation anti-androgenic drugs like Abiraterone, Enzalutamide, Darolutamide and Apalutamide

TABLE 2. Potential oncogenes involved in prostate cancer progression and therapeutic resistance.

Oncogene	Molecular Type	Affecting prostate cancer hallmarks process and pathogenic events	Reference
AR	Nuclear Receptor	Involved in most of prostate cancer associated hallmark processes and pathogenic events including castration resistance and bone metastasis	Supplementary File-Sheet_2
TMPRSS2	Serine Protease	Self-sufficiency in growth signaling	
ERG-1	Transcription Factor	Self-sufficiency in growth signaling	
STAT3	Transcription Factor	Self-sufficiency in growth signaling, angiogenesis, metastasis, castration resistance	
AR-V7	Nuclear Receptor	Self-sufficiency in growth signaling (cell proliferation, cell survival), Castration Resistance, Metastasis, Cell death resistance, Metabolic Reprogramming	
c-MYC	Transcription Factor	Self-sufficiency in growth signaling (cell proliferation, Cell growth, cell survival), Castration Resistance, Androgenic Response, Cell death resistance (enz), Metabolic Reprogramming, Metastasis, Enabling Replicative Immortality	
EZH2	Transcription Regulatory Protein	Self-sufficiency in growth signaling (cell proliferation), Cell death resistance, Metastasis, Castration Resistance, Androgenic Response, Angiogenesis, Metabolic Reprogramming	
BCL2	Adapter Protein	Cell growth, Cell death resistance, Metastasis	
CXCR4	G protein coupled receptor	Cell growth, Cell proliferation, Tumor Microenvironment, Metastasis, Cell death resistance, Androgenic Response	
CTNNB1	Adhesion Molecule	Cell proliferation, Cell growth, Metastasis, Cell death resistance (radiation), Angiogenesis, Castration Resistance,	
TWIST1	Transcription Factor	Metastasis, Inflammation, Castration Resistance, Androgenic Response	
YB-1	Transcription Factor	Metastasis, Castration Resistance, Cell death resistance	
VAV3	Guanine Nucleotide Exchange Factor	Self-sufficiency in growth signaling (cell survival, cell growth), Castration Resistance, Metastasis, Androgenic Response, Androgen Independence	
PIM	Serine/Threonine Kinase	Self-sufficiency in growth signaling (Cell survival), Metastasis, Castration Resistance, Cell death resistance, Genomic Instability	
PRKCE	Serine/Threonine Kinase	Cell proliferation, Cell growth, cell survival, Metastasis, Androgen Independence	
CAV1	Structural Protein	Cell growth, Cell death resistance, Metastasis, Angiogenesis, Castration Resistance, Metabolic Reprogramming	
EGFR	Receptor Tyrosine Kinase	Cell proliferation, Cell growth, Metastasis, Castration Resistance, Metabolic Reprogramming	
FYN	Tyrosine Kinase	Cell proliferation, Cell growth, Metastasis	
MET	Receptor Tyrosine Kinase	Self-sufficiency in growth signaling (cell proliferation), Metastasis, Tumor Microenvironment, Cell death resistance, Castration Resistance, Androgen Independence	
IGF1R	Receptor Tyrosine Kinase	Self-sufficiency in growth signaling (Cell growth), Metastasis, Angiogenesis, Metabolic Reprogramming	
HER2	Receptor Tyrosine Kinase	Self-sufficiency in growth signaling (cell proliferation, cell survival), Castration Resistance, Metastasis, Cell death resistance, Androgenic Response	
PAR1	G protein coupled receptor	Self-sufficiency in growth signaling (cell proliferation, cell survival), Metastasis	
EGF	Growth Factor	Self-sufficiency in growth signaling (cell proliferation, cell survival), Castration Resistance, Metastasis, Cell death resistance, Androgenic Response	
HGF	Growth Factor	Self-sufficiency in growth signaling, Metastasis, Castration Resistance, Angiogenesis	
IGF1	Growth Factor	Cell growth, Androgenic Response, Metastasis	
IGF2	Growth Factor	Self-sufficiency in growth signaling (cell survival), Cell death resistance, Metabolic Reprogramming	
FGFR1	Receptor Tyrosine Kinase	Angiogenesis, Inflammation, Metabolic Reprogramming, Castration Resistance, Tumor Microenvironment, Metastasis	

are usually used for CRPC patients with an improvement in patient's health related qualities of life [18–22]. Although, existing reports indicates the prior treatment with Docetaxel does not provide any significant impacts in Abirateone or Enzalutamide activities but Enzalutamide treatment critically mediates the development of cross-resistance against Docetaxel [25, 26]. On the other hand, Docetaxel resistant prostate tumor are intrinsically cross-resistant to other taxen based drug Cabazitaxe during CRPC treatment [27]. The current knowledge based on five retrospective and two prospective clinical trials over 911 metastatic CRPC patients critically suggests for an Abirateone plus Prednisone-Enzalutamide treatment sequence that provides better progression free survival (PFS) than an order of first Enzalutamide administration followed by an Abiraterone plus Prednisone application [28]. But, in point of overall survival (OS), no significant levels of survival advantage was found in each of the corresponding five retrospective studies [28]. In addition, the trends of therapeutic resistance also appears during treatment with anti-androgen drugs,

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TABLE 2. Continued.

Oncogene	Molecular Type	Affecting prostate cancer hallmarks process and pathogenic events	Reference
FAK	Tyrosine Kinase	Self-sufficiency in growth signaling (Cell growth), Metastasis, Castration Resistance, Angiogenesis, Cell death resistance, Androgen Independence	
PXN	Cytoskeletal Associated Protein	Self-sufficiency in growth signaling (cell proliferation), Androgenic Response, Metastasis	
LPXN	Adapter Protein	Androgenic Response, Metastasis	
FHL2	Adapter Protein	Androgenic Response, Castration Resistance, Metastasis	
CFLAR	Adapter Protein	Self-sufficiency in growth signaling (cell survival), Cell death resistance	
PIRH2	Ubiquitin Proteasome System Protein	Androgenic Response	
PIM1	Serine/Threonine Kinase	Self-sufficiency in growth signaling (Cell growth, cell survival), Metastasis, Castration Resistance, Cell death resistance, Inflammation, Androgenic Response	
PCA3	Enzyme: Reductase	Androgenic Response, Metastasis	
GBX2	DNA Binding Protein	Self-sufficiency in growth signaling (Cell growth), Metastasis	
EPHA2	Receptor Tyrosine Kinase	Self-sufficiency in growth signaling (cell proliferation), Metastasis	
SATB1	Transcription Factor	Self-sufficiency in growth signaling (cell proliferation, Cell growth, cell survival), Metastasis	
PRKCD	Serine/Threonine Kinase	Androgenic Response, Metabolic Reprogramming	
FABP5	Transport Protein	Self-sufficiency in growth signaling (cell proliferation, Cell growth, cell survival), Metabolic Reprogramming, Castration Resistance	
PCNT	Cytoskeletal Protein	Self-sufficiency in growth signaling (Cell growth), Angiogenesis, Genomic Instability	
12-LOX	Enzyme: Oxidoreductase	Self-sufficiency in growth signaling (cell proliferation, cell survival), Metastasis	
LAMP1	Membrane Protein	Self-sufficiency in growth signaling (cell proliferation), Metastasis	
AURKA	Serine/Threonine Kinase	Self-sufficiency in growth signaling (cell proliferation, Cell growth), Metastasis, Castration Resistance	
BCOX1	Unclassified	Self-sufficiency in growth signaling (cell proliferation), Metastasis	
CDK1	Serine/Threonine Kinase	Self-sufficiency in growth signaling (cell proliferation, cell survival), Cell death resistance (Enz), Castration Resistance, Metastasis	
CCNB1	Cell Cycle Control Protein	Self-sufficiency in growth signaling (cell proliferation), Castration Resistance	
HEC1	Cell Cycle Control Protein	Self-sufficiency in growth signaling (Cell growth, cell proliferation), Cell death resistance	
MED12	Transcription Regulatory Protein	Castration Resistance, Genomic Instability, Metastasis	
PBOV1	Unclassified	Self-sufficiency in growth signaling (cell proliferation)	
HOXB13	Transcription Factor	In sensitivity to anti-growth signaling, Castration Resistance, Metastasis, Cell death resistance	
ADCY10	Adenylate Cyclase	Self-sufficiency in growth signaling (cell proliferation), Cell death resistance (radiation)	
ID-1	Transcription Regulatory Protein	Self-sufficiency in growth signaling (cell survival, cell growth), Cell death resistance, Androgen Independence, Metastasis	
AGR2	Unclassified	Self-sufficiency in growth signaling (cell proliferation), Cell death resistance, Metastasis	
SKA1	Unclassified	Self-sufficiency in growth signaling (cell proliferation), Metastasis, Genomic Instability	
MAK	Unclassified	Genomic instability	
NCOA3	Transcription Regulatory Protein	Self-sufficiency in growth signaling (cell proliferation, cell survival), Cell death resistance, Androgenic Response, Metastasis	
FOXM1	Transcription Factor	Self-sufficiency in growth signaling (cell proliferation), Cell death resistance, Metastasis, Androgenic Response	
SPAG9	Membrane Protein	Self-sufficiency in growth signaling (Cell growth), Metastasis, Angiogenesis	

like around 20%-40% of CRPC patient's produces primary resistance against Enzalutamide and Abiraterone treatment and most of the patients ultimately acquire secondary resistance [10, 14, 15]. For this major reasons, currently many experts suggests that application of Enzalutamide and Abiraterone shoud be considered only for a highly selected group of patients instead of total metastatic CRPC associated patient's populations [29]. Furthermore, existing reports suggests for the emergence of cross-resistance associated events for both Abiraterone and Enzalutamide during their therapeutic period [30]. At the same time, prostate cancer which are resistant to Abiraterone and Enzalutamide treatment also exhibits cross-resistance against Apalutamide and Darolutamide [30]. By recognizing all these major facts, recently many urologists critically suggests to avoid next generation androgen targeting agents in sequence for most of the advanced prostate cancer patients [29]. In addition to these challenging aspects, there are other serious issues including toxicity burdens, severe treatment side effects like sexual dysfunction and high costing of the entire treatment procedure due to use of highly expensive treatment modalities [31–34]. For increasing efficacies

TABLE 2. Continued.

Oncogene	Molecular Type	Affecting prostate cancer hallmarks process and pathogenic events	Reference
NSD2	Transcription Regulatory Protein	Self-sufficiency in growth signaling (cell proliferation, cell survival, cell proliferation), Androgenic Response, Metastasis	
ETV1	Transcription Factor	Self-sufficiency in growth signaling (Cell growth), Metastasis, Androgenic Response	
RPL31	Ribosomal Subunit	Self-sufficiency in growth signaling (Cell growth)	
PLK1	Serine/Threonine Kinase	Cell death resistance, Castration Resistance, Androgenic Response	
FGF-2	Growth Factor	Self-sufficiency in growth signaling (cell proliferation), Genomic Instability, Tumor Microenvironment, Metastasis	
LIV1	Membrane Transport Protein	Metastasis	
SPINK1	Protease Inhibitor	Castration Resistance, Metastasis	
HSP27	Chaperone	Androgenic Response, Castration Resistance, Metastasis	
CLU	Complement Protein	Self-sufficiency in growth signaling (Cell growth), Metastasis, Cell death resistance, Castration Resistance	
MiR-301a	Micro-RNA	Metastasis, Cell Death Resistance	
ITGB4	Adhesion Molecule	Self-sufficiency in growth signaling (cell survival), Androgenic Response, Metastasis,	
SMAD2	DNA Binding Protein	Self-sufficiency in growth signaling (cell proliferation), Castration Resistance, Metabolic Reprogramming, Metastasis	
SMAD3	Transcription Regulation	Self-sufficiency in growth signaling (cell proliferation, cell growth), Metastasis, Angiogenesis, Androgenic Response	
MMP-2	Enzyme: Protease	Metastasis	
MMP-9	Enzyme: Protease	Metastasis, Angiogenesis	
AQP3	Water Channel	Metastasis	
SIRT1	Enzyme: Deacetylase	Self-sufficiency in growth signaling (cell survival), Cell death resistance (Autophagy), Metastasis	
GOLM1	Transport Protein	Self-sufficiency in growth signaling (cell survival), Cell death resistance, Metastasis	
HPN	Serine Protease	Metastasis, Cell death resistance	
ST14	Serine Protease	Metastasis	
CENPF	Cell Cycle Control Protein	Self-sufficiency in growth signaling (cell proliferation, cell growth), Metastasis	
ATM	Serine/Threonine Kinase	Cell death resistance, Metastasis	
ASAH1	Enzyme: Hydrolase	Cell death resistance, Self-sufficiency in growth signaling (Cell growth)	
LDH5	Enzyme: Dehydrogenase	Self-sufficiency in growth signaling (cell survival), Cell death resistance	
ABCB1	Transport Protein	Cell death resistance, Castration Resistance	
EpCAM	Adhesion Molecule	Cell death resistance	
GRP78	Chaperone	Self-sufficiency in growth signaling (cell proliferation), Metastasis, Castration Resistance	
PC-1	Unclassified	Castration Resistance	
4E-BP1	Translation Regulatory Protein	Self-sufficiency in growth signaling (Cell growth), Castration Resistance	
MED1	Transcription Regulation	Self-sufficiency in growth signaling (cell survival, cell proliferation), Inflammation, Castration Resistance	
PSGR	G protein coupled receptor	Self-sufficiency in growth signaling (cell proliferation, cell growth), Inflammation, Metastasis (Invasion)	
EGR3	Transcription Factor	Self-sufficiency in growth signaling (cell proliferation) Inflammation	
Mir-210	Micro RNA	Self-sufficiency in growth signaling (cell proliferation), Bone Metastasis, Tumor Microenvironment, Angiogenesis, Cell death resistance	
MYCN	Transcription Factor	Cell death resistance, Castration Resistance	
FASN	Enzyme: Synthase	Castration Resistance, Metabolic Reprogramming, Cell death resistance	
BCL-XL	Adapter Protein	Cell death resistance, Castration Resistance	
MCL1	Chaperone	Cell death resistance, Castration Resistance	
MED15	Transcription Regulation	Castration Resistance	
SOCS3	Adapter Protein	Cell death resistance, Inflammation	
TGFA	Growth Factor	Cell proliferation, Cell growth, Bone Metastasis	
HSF1	Transcription Factor	Cell survival, cell growth), Metastasis, Cell death resistance	
PRDX-3	Enzyme: Peroxidase	Self-sufficiency in growth signaling (cell survival)	
5-LOX	Enzyme: Lipase	Self-sufficiency in growth signaling (cell survival, cell proliferation)	

and determining the optimal sequencing strategies among currently used therapeutics, there is an urgent need to get a comprehensive view over these resistance mechanisms in prostate cancer.

TABLE 3. "Prostate cancer progression pathways" profiling.

Progression pathways and Terrain Factors	Involved prostate cancer hallmarks	Key mediators of corresponding progression pathways and terrain factors	Reference
Cell Proliferation	Self-sufficiency in growth signaling, Castration Resistance	AR, EGFR, IGF1R, FGFR1, CXCR4, c-MET, TMPRSS2, ERG, PSA, NF-kB, MED1, MED15, TGFB, SMAD2, SMAD3, c-MYC, PRKCE, STAT3, PI3K, AKT, FYN, RHOA, CTNNB1, SHC, HSP90, SRC, RAC1	Supplementary File-Sheet_3
Apoptosis	Cell death resistance, Castration resistance	BCL2, BCL-XL, MCL1, CLU, HSP27, PRKCE, FHL2, CAV1, FOXM1, CTNNB1, STAT3, NF-kB, HSF1, IGF1R, IGF1, IGF2, EGFR, TGFA, TCTP, GPX2	
Angiogenesis	Angiogenesis, Metastasis	PI3K, AKT, JNK, AP-1, MTOR, NF-kB, PXN, FAK, STAT3, HIF1A, c-SRC, GP91PHOX, P22PHOX, PRKCA, PRKCD, ANG1, AKR1C3, COX2, VEGFA, VEGFC, NOS, LOX-1, HO-1, SPAG9, 12-LOX, PGK1, IL-6, IL-8, TIE2	
Cell to cell communication	Self-sufficiency in growth signaling, Angiogenesis, Metastasis, Castration resistance	OPN, CDH2, CDH1, ITGB3, ITGB1, ITGA5, AGR-2, BAG3, VNR, RACK1, TROP-2, FAK, PXN, RAC1, JNK, BCAR1, PTK6, HSP90, LPXN, SNAIL, SLUG, TWIST1, SELE, FN1	
Bone Metastasis	Metastasis, Castration resistance	EPHA2, VAV3, RAC1, MMP-2, MMP-9, MMP-14, NF-kB, STAT3, AR, RANK, RANK-L, CXCR4, PI3K, AKT, HER2, CCL5, ETS1, SHH, PTHRP, DKK1, CTSL, CTSK, BMP2, OPG, IL-8, WISP1, MCP1, IGFBP5	
Immune Evasion	Avoidance of immune destruction	PD-L2, PD-L1, PD-1, FAS, EGF, EGFR, PI3K, AKT, MTOR, NF-kB, ARG1, ARG2, NOS2, CSF1, IL1B, TGFB1, IL-10, IL18BP, DIAPH3, CD-200, IL-23A, IGHA1, IGHA2	
Immortality	Enabling replicative immortality	IGF1R, IGF1, PI3K, AKT, STAT3, c-MYC, BMI1, ESR2, FADD, P23, HSP90, NOS, HIF1A, HIF2A, PRKCA, PARM-1, AGR2, ATM, AR, E2F1, IGFBP-2	
Neuroendocrine differentiation	Castration resistance	FYN, MYCN, AURKA, PKA, CREB, CTNNB1, TMPRSS2, ERG, ETV1, ATF2, MDK, TGFA, CGA, TUBB3, IFNG, IL-6, SNAIL, TIMP1, VIP, ERK1, ERK2, WNT-11	
Inflammation (Terrain factors)	Tumor promoting inflammation	NF-kB, STAT3, STAT1, PRKCE, EGR3, IL-6, IL-8, AIM2, ASC, EZH2, MED1, PSGR, TNFA, IL6ST, COX2, IFNB, IFNG, TLR9, PTX3	
Stress induction (Terrain factors)	Tumor Microenvironment, Metastasis, Castration resistance	STAT5A, STAT3, EIF4E, HSP27, TCTP, MAOA, HIF1A, RACK1, PKM2, SRC, TRPM8, CAIX, COX2, DEC1, EGFR, EGF, YB-1, CLU, NF-kB, NOX, BLT2, RUNX2, BCL2, SPHK1, SSAT	
Oxidation (Terrain factors)	Metabolic reprogramming, Castration Resistance	HIF1A, PKM2, HK2, ARRB1, IGF1, IGF1R, CAV1, PI3K, AKT1, AMPK, c-MYC, SK1, OGT, PGC1A, AR, LDH5, ACOX3, GLUT1, GLUT3, AMACR, SCD1, ELOVL7, FASN, PKM2, PFK, KLHL20	
Coagulation (Terrain factors)	Metastasis	PT, FGG, PAR1, PAR2	
Glycemia (Terrain factors)	Self-sufficiency in growth signaling	IGFBP2, IGF1, MiR-301a, DPP4, LEP, LEPR, IGF1R, INSR, INS	

3.2 Real facts behind prostate cancer therapeutic unsuccessfulness

Existing reports indicate a strong presence of post therapeutic resistance phenomenon for most of the currently used therapeutics during CRPC treatment [12–16]. Around 136 key mediators are involved for the overall development of these resistance events during different stages of CRPC treatment against Docetaxel, Paclitaxel, Cabazitaxel, Enzalutamide, Abiraterone and radiation therapy [Table 1]. A wide variety of factors ranging from activation of efflux pump, oxidative stress, hypoxic tumor microenvironment, immune checkpoint activation, interactions between prostate tumor cell and cancer associated fibroblasts and activation of androgen receptor mediated signaling likely modulates the genesis of these resistance phenomenon. Here, we provides a very brief overview for some of these resistance events.

Docetaxel resistance- Docetaxel is a microtubule targeting compound, the first chemotherapeutic drug approved for the treatment of advanced prostate cancer with a considerable three months of survival advantages [12–14]. Although, Docetaxel treatment in many patients initially produces a remarkable clinical responses, but clinical effectiveness is often compromised due to genesis of primary and acquired resistance over Docetaxel after its therapy [12–14, 27, 35, 36]. Around 55 molecular drivers are markedly associated with the development of Docetaxel resistance in CRPCs by numerous number of ways [Table 1]. The most impor-

tant resistance mechanisms are ERG rearrangements, loss of microtubule bundling associated with tubulin alterations, activation of drug efflux pump ABCB1, activation of cancer stem cell associated NOTCH and Hedgehog pathways, hyper-activation of PI3K/AKT pathways, centrosome clustering by motor protein KIFC1, activation of growth factor associated signaling mediated by insulin receptor (INSR) insulin -like growth factor receptor-1 (IGF1R), epidermal growth factor receptor (EGFR) and suppression of Docetaxel efflux by testosterone and associated androgen receptor mediated signaling [12–14, 35, 36].

Paclitaxel resistance- Paclitaxel is another taxane based chemotherapeutic agents used for first line treatment of CRPC. But, however the occurrence of severe levels of paclitaxel resistance has been reported during CRPC treatment [13, 14]. Nearly 28 key molecular drivers are involved for the emergence of Paclitaxel resistance like phenomenon in prostate cancer in a context specific manner. The most common signaling axis for prostate cancer development like PI3K/AKT RAF1/ERK and androgen receptor mediated signaling pathways plays an intrinsic role in CRPC associated paclitaxel resistance [37–39]. But, however a number of critical oncogenic mediators such as Clusterin (CLU), Yamaguchi Sarcoma viral homologue 1 (YES1) and Sex determining region Y-box 2 (SOX2) mediates a significant functions in promotion of paclitaxel resistance in a patient specific manner. The corresponding critical events in chemo resistances are YB-1 mediated trans-activation of Clusterin (CLU), activation of ribosomal S6 kinase (RSK), ETS1 transcription factor mediated transcriptional up-regulation of drug transporter MDR1, SOX2 mediated induction of G1/S phase transition in cell cycle, estrogen dependent activation of PHB adaptor protein and MiR-302a mediated regulation of BCL2, BAX and P21 [37–43].

Enzalutamide Resistance- Enzalutamide is a next generation androgen targeting agent that is currently most commonly used for CRPC treatment after failure of androgen deprivation therapy. Although, Enzalutamide treatment in many cases significantly improves the overall survival in CRPC patients [12, 15]. But, the efficacies of Enzalutamide is severely challenged by the acquisition of significant levels of both primary and adaptive resistances by multiple ways and in this regard more than 25 proteins have been reported so far [Table 1]. Basically, the event of Enzalutamide resistance occurs through active participations of both androgen dependent and independent ways in a context and case specific ways [44, 45]. Hyper activation of androgen receptor by means of its overexpression (around 80% of CRPC patients), amplification, mutation is more commonly observed in CRPC patients during the period of Enzalutamide treatment than in treatment naïve conditions [44]. This hyper activated androgen receptor mediated signaling in association with its splice variants (AR-V7) and altered steroidogenesis are mainly involved for the development of adaptive resistance to Enzalutamide chemotherapy in CRPC patients. In addition, several androgen independent events such as PI3K/AKT pathway mediated activation of glucocorticoid receptor (GR), CXCR7 induced MAPK/ERK signaling, hyper activation of HER2/HER3 signaling and critical modulation of transcriptional master regulator like STAT3 and NF-KB also plays a context specific important roles in these types of therapeutic resistance [44–47].

Abiraterone Resistance- Abiraterone Acetate is a next generation androgen biosynthetic pathway targeting drug often used for treatment of metastatic CRPC patients in post-Docetaxel period. However, primary resistance to Abiraterone is frequently observed in around one third of all patients and secondary resistance appears in most of the patients after 15 months [10, 14, 15]. According to the recent information, the phenomenon of Abiraterone resistance is critically triggered by 8 key driver proteins in metastatic CRPC patients [Table 1]. The most common mechanisms of Abiraterone resistances are reactivation of androgen receptor (AR) associated signaling, up-regulation of CYP17A1 gene, alternative ligand production and generation of androgen receptor (AR) splice variants, which functions as a ligand independent transcription factor [14, 15]. CYP17A1, the key regulator of androgen biosynthesis are up-regulated after an Abiraterone treatment and plays a potential role in this type of chemo resistance development [14, 15]. In addition, hyper-activation of androgen receptor (AR) and heterogeneous expression of its splice variants AR-V9 and AR-V7 in metastatic castration resistant disease condition also plays a significant role in acquisition of Abiraterone resistance through promotion of ligand independent prostate tumor growth [48, 49].

Basically, current therapeutic inconsistencies for CRPC can be explained by several other critical factors which not only increases the complexities of these diseases but also are centrally responsible for observed ineffectiveness of available treatment processes during late stage of CRPC progression. Fundamentally, CRPC progression can be characterized by its extreme levels of inter-tumor & intra-tumor heterogeneity [21–23], remarkable variability's in clinical behavior along with mechanistic complexities and presence of redundancies in tumor cell signaling pathways driven by the key functional interplay of multiple oncogenes [8, 50–53]. In fact, these prostate cancer patient specific intra-tumor heterogeneities also provides the essential challenges for attaining desired clinical effectiveness during metastatic prostate cancer treatment [54, 55]. A recent studies on genomic aberrations from advanced prostate cancer patients critically suggest for the existence of oncogene centric deregulation signatures during the development of aggressive features in prostate cancer like bone metastasis and castration resistance from primary prostate cancer by following current treatment [56]. In a number of patients, it has been found that these genomic instabilities are mainly focused on the central prostate cancer driver like AR, RB1, TP53, ETS, CTNNB1, RAF, APC and PI3K/AKT associated pathways. These genomic instabilities are largely responsible for acquisition of intra tumor heterogeneities and metastatic capabilities during prostate

cancer progression [54–56]. By considering these essential facts, it can be factually assumed that the current so called "one size fits to all" strategy cannot provide the necessary practical measures to successfully combat over castration resistant state of the disease. An ultimate emergence of prostate cancer therapeutic resistance over all current FDA approved drugs along with recent failure of dendritic cell based prostate cancer vaccine PROSTVAC (PSA-TRICOM) and CTLA-4 targeting Ipilimumab in clinical trials of asymptomatic or minimally symptomatic metastatic CRPC patients conclusively support this facts [15, 16, 57, 58].

4. Future ultimate aim in prostate cancer research

Trends in current research strongly suggests that development of CRPC should be visualized as a personalized basis and its corresponding treatment process must be done accordingly [10, 11, 33, 34, 59]. The future therapeutic approaches must provide right treatment in a right patient in a right time i.e. the treatment decision must be taken according to the genomic landscape, molecular profiling and pathological state of the CRPC patient [33, 34, 59–62]. Although it's a much generalized strategy in precision medicine, there is a considerable need to find a better applicability of these strategies in a castration resistant disease specific manner. For that purpose, from a practical point of view the principal task demands for identification of potential CRPC related genes, corresponding activated pathways related information's, components of tumor-immune microenvironments and knowledge over resistance pathways resulting from the application of currently FDA approved drugs [13, 33, 34]. With an appropriate case specific application of this combined knowledge in association with current omics technologies and a large pool of recently developed therapeutic agents, it may be possible in future to find the basis of ultimate therapeutic combinations which will markedly upgrade patient's health related quality of life along with overall survival rate in CRPC patients. To attain this basic demand, there is a critical need to develop prognostic and therapeutic biomarkers which will guide for proper patient stratification and find effective therapeutic strategies for different subset of metastatic CRPC patients [59–61]. And finally, development of molecular sub classification system and their specific clinical trial designing in prostate cancer will potentially assist in proper evaluation of patient's therapeutic responses and identification of predictive biomarker, which may play an instrumental role in precise assessment of patient's clinical responses [63, 64].

4.1 Principal challenges in current prostate cancer precision medicine

The much desired personalization of prostate cancer associated treatment approaches has just started with a great promise to provide much better risk factor based patient stratification and efficient therapeutic predictions among CRPC patients [59–62]. Recent advents of next generation sequencing based genomic approaches in CRPC has revolutionized our understanding of CRPC associated clinical spectrum by an extensive characterization of its underlying significant genomic, transcriptomic and epigenomic alterations [33, 34, 65]. Furthermore, the current development of 3D prostate organoid culture and CRPC patient derived xenografts provides a better opportunity to study different aspects of advanced prostate cancer progression like its key cellular interactions, underlying signaling mechanisms and drug sensitivity screening [66–68]. In spite of these technological improvements, successful implementations of precision medicine in advanced prostate cancer remains a formidable challenge due to presence of several practical limitations which needs to be properly addressed [61, 62].

The first and most important challenge arises owing to lack of transition from genome driven patient based mutational landscape identification to its corresponding therapeutic selection and patient specific clinical implementation [33, 34, 65]. Current 'prostate cancer precision medicine' is almost synonymous with 'genomic medicine' which explores somatic genetic alterations in patients by NGS or WES based methods [33, 60, 69, 70]. But, functional and clinical consequences of such frequent genetic alterations in majority of cases is not properly known and it most significantly impacts subsequent clinical decision making processes to find right therapeutic combinations in corresponding cases. This at least effects three considerable factors that are pivotal for determining therapeutic efficacies, namely prioritization's of somatic alterations towards targeted therapy [65, 70], designing the optimal therapeutic sequencing for right patient at right time from present therapeutic platform [12, 24, 71, 72] and biomarker based patient stratification [64, 73].

Second major challenge arises by the presence of significant levels of heterogeneity and multifocality in advanced prostate cancer which critically restricts both application of NGS based approaches towards therapeutic prediction in CRPC and attaining therapeutic efficacies during molecularly targeted therapy [33, 34, 65]. Third challenge arises due to several complex serious issues like accurate translation of multiple omics data and construction of corresponding infrastructure in clinical setting [74, 75]. Fourth challenge includes technical limitations associated with biopsy of tumor tissues from bone metastatic prostate cancer patients which critically restricts its accurate next generation sequencing and therapeutic resistance monitoring [33, 65]. As a fact, current transrectal biopsy based prostate cancer detection technique is severely criticized for its inherent sampling bias, lack of standardization and insufficiencies in capturing total genetic landscape in prostate tumor [34, 76, 77]. Fifth challenge results from an increased cost of current prostate cancer treatment which makes the issue really questionable to implement further precision medicine program in most of the countries in the world [33]. This high level of costing in prostate cancer precision medicine is due to use of costly chemotherapeutics, introduction of next generation based

techniques and requirement of expensive patient derived xenografts (PDXs) and personalized in vitro drug testing which makes the scenario almost unaffordable by 80% of the world populations ranging from developed to developing countries including India [78, 79].

5. Role of major oncogenes in castration resistant (CRPC) prostate cancer advancement

Personalized molecular and genomic profiling may provide the true basis for future individualized treatment selection and subsequent sequencing procedures [80–83]. The development of prostate tumorigenesis and its metastatic progression is significantly linked by a number of specific genomic alterations that mainly includes gene fusions, amplifications, over expressions and DNA copy number variations [33, 73, 81, 82]. These recurrent genomic alterations in association with transcriptional reprogramming creates a number of prostate cancer driver oncogenes that plays a fundamental role in tumorigenic progression of prostate cancer, its further pathological expansions and acquisition of its therapeutic resistance [82–85]. Current research strongly supports for the presence of 103 potential oncogenes that plays the characteristic leading role in advancement of disease recurrence and emergence of castration resistance [Table 2]. Many of these oncogenes are intrinsically associated with pathophysiological progression of prostate cancer along with its hallmarks manifestations and a few of them like TMPRSS2-ERG are observed in half of advanced prostate cancer cases [86]. Patient specific identification of these oncogenes may provide a profound critical roles in future therapeutic selection and corresponding therapeutic and prognostic biomarkers development. Out of these 103 oncogenes, 6 oncogenes along with androgen receptor plays a characteristic leading roles for prostate cancer advancement. This core oncogenes are mostly important in point of metastatic CRPC progression, therapeutic interest, current clinical trials and future proposals from the ground of personalized prostate cancer treatment. Here we very briefly discuss on the role of these core oncogenes along with recent updates.

ERG- ETS related gene (ERG) is the most frequently found oncogene in prostate tumor, a member of ETS transcription factor which typically follows an overexpression during the course of prostate tumorigenesis and is centrally involved in prostate cancer advancement through its major role in metastatic progression [86–89]. The overexpression of ERG is observed in significant number of prostate cancer and its overexpression actually results from a genetic fusion event with the androgen responsive TMPRSS2 gene [86, 87]. ERG oncogenes are critically responsible for the loss of cell polarities, alterations in cell adhesion, induction of epithelial mesenchymal transition (EMT) and loss of E-cadherin expression in prostate tumor [87]. ERG is mainly involved in prostate cancer associated cell mobility's, cell invasions and bone metastasis through activation of a number of key metastatic drivers like matrix metalloproteases (MMP1, MMP3, ADAMTS1), WNTs, TGFB, EZH2, SOX9, VEGFR2, ZEB1/ZEB2, RHOA, CXCR4 and plasminogen activator pathways [86, 88]. Currently, several small molecular inhibitors like YK-4-279, VPC-18005 and ERGi-USU have been developed for therapeutic targeting of ERG and several leading researches are going on to further evaluation of their therapeutic potentials [86–88].

TMPRSS2- TMPRSS2 is an androgen responsive prostate specific trans-membrane serine protease, which is most commonly found in localized and advanced prostate cancer [86, 89, 90]. The specific genomic rearrangement events between the first exon(s) of TMPRSS2 with ERG oncogene results in TMPRSS2-ERG fusion product, that is often observed in nearly half of advanced prostate cancer patients [86]. Both TMPRSS2-ERG and TMPRSS2 itself plays a major oncogenic role in aggressive manifestations of metastatic CRPCs [90, 91]. For example, several lines of pre-clinical and clinical studies suggests for the existence of an oncogenic signaling network involving TMPRSS2, androgen receptor (AR), hepatocyte growth factor (HGF) and c-MET that critically induces early steps of metastatic initiation in association with marked switching of N-cadherin production [91]. In fact, current research strongly supports for the TMPRSS2 associated driver role in overall modulation of metastatic behavior acquisition by prostate cancer cells [86, 89–92]. On the other hand, TMPRSS2-ERG fusion typically enhances bone metastatic prostate cancer associated cell growth, proliferation and metastatic spread [90]. Most crucially, the fusion product obtained from TMPRSS2-ERG genomic rearrangement locally produces androgen which in turn supports for the metastatic growth of prostate tumors in bone microenvironment [90]. For these essential reasons, currently a number of research is involved to use TMPRSS2-ERG associated fusion product as predictive biomarker in order to target androgen receptor centric signaling network in metastatic CRPC patients [92].

STAT3- STAT3 transcription factor plays a pivotal role for modulation of several core oncogenic signaling molecules and corresponding onco-protein networks operated across a range of prostate cancer hallmark activities. Signal Transducer and Activator of Transcription 3 (STAT3) is frequently overexpressed in CRPC and believed to be centrally associated with prostate cancer related self-sufficiency in growth signaling, cell death resistance, metabolic reprogramming, avoidance of immune destruction, angiogenesis, metastasis and castration resistance [93, 94]. Master regulator STAT3 is closely involved in acquisition of prostate cancer associated castration resistance and chemo-resistance through reactivation of androgen receptor mediated signaling and integration of multiple essential signals mediated through growth factors, cytokines, adaptor proteins and various kinase classes of enzymes [94–96]. Current research suggests that STAT3 regulates a number of prostate cancer driver proteins in various contexts including BCL2, BCL-XL, MCL-1, VEGF, FGF and c-MYC [93–96]. Considering its potential involvement in prostate cancer advancement, a number of natural products like Celastrol, Curcumin, Capsaicin, Caffeic

acid, Curcubitacin, Emodin and small molecular inhibitors including GPA500, STA-21, AZD1480 and AG-490 have demonstrated considerable efficacies in therapeutic targeting of STAT3 [94–96].

EGFR- EGFR is an oncogenic receptor tyrosine kinase that is often overexpressed during prostate cancer progression and intrinsically linked with both the early phases of prostate tumorigenesis and late phase of CRPC developments [97]. A number of ligands including EGF, TGFA, Epiregulin and Amphiregulin have been reported to activate epidermal growth factor receptor (EGFR) during prostate cancer development. Although, EGF functions as the predominant ligand for EGFR in early phases of localized prostate cancer formation but during late phase of metastatic CRPC development, TGFA plays a characteristic leading role in EGFR activation [98]. EGFR is primarily responsible for constitutive activation of oncogenesis through subsequent stimulation of diverse essential signaling mediators in order to trigger self-sufficiency in growth signaling through enhancement of prostate cancer cell growth and proliferation programs [99]. EGFR plays the most critical modulatory role during the development of androgen independence through post translational modification of androgen receptor (AR) in order to reactivate its downstream signaling in castration resistant condition [100]. In addition, TGFA mediated activation of EGFR associated oncogenic signaling also plays a potential role in remodeling of bone microenvironment during prostate cancer associated metastatic progression [98]. For these basic role in aggressive prostate cancer development, EGFR targeting therapies are currently believed as an ideal approach for treatment of ErbB-2 dependent prostate cancer [101]. Several pre-clinical studies on mouse model and clinical trials have indicated limited efficacies of EGFR targeting therapeutic inhibitors like Gefitinib, Erlotinib and BIBW-2992 due to overproduction of EGFR ligands by prostate tumor and its stromal microenvironments [101]. Currently, a number of EGFR targeting combination therapy and immunotherapy based approaches are evaluating their efficiencies for treatment of hormone refractory prostate cancer [97–101].

HER2- Human epidermal growth factor receptor 2 (HER2) plays a crucial role for supporting different oncogenic aspects during the aggressive development of prostate cancer. Receptor tyrosine kinase HER2 is generally overexpressed during prostate cancer advancement as a result gene amplification and critically drives the formation of CRPC by means of androgen independent androgen receptor signaling activations [96, 102]. HER2 hyperactivation is most typically mediated through androgen stimulated P66SHC/ROS induced inhibition of prostatic acid phosphatase (cPAcP), a critical regulator of HER2. Basically, HER2 is an ErbB family member and activates a number of key signaling molecules including androgen receptor (AR) for stimulation of cell proliferation, survival and migrations like activities during prostate tumorigenesis [102]. HER2 mediated signaling is specifically modulated by cholesterol accumulations, formation of lipid rafts and CXCR4 mediated signaling in context of oncogenic activation of downstream signaling effectors [102, 104]. HER2 in association with RANKL activation mediates the most crucial functions during androgen independent growth and invasion of prostate tumor in distant bone microenvironments [102, 105]. Although, a number of HER2 targeting strategies have been developed, but most of the concerned pre-clinical and clinical studies clearly indicates a limited efficacies of HER2 inhibitors in CRPC patients. For these major reasons, currently combination therapy and immunotherapy based approaches are investigating the clinical effectiveness of HER2 inhibition in advanced prostate cancer [102, 104].

MYC- Proto-oncogene MYC is a master transcriptional regulator that activates a number of hallmarks associated patho-physiological processes during prostate cancer development. MYC functions as a prototypic oncogenic driver of prostate cancer pathogenesis through inducing cell proliferation, metastasis, metabolic reprogramming, replicative immortalization and castration resistance [105, 106]. MYC overexpression as a result of genomic amplification of 8q/8q24 chromosomal region is generally observed nearly 30% of localized prostate cancer and around 50% of advanced prostate cancer with poor levels of prognosis [105, 106]. It has been found that overexpression of MYC proto-oncogene is generally linked with TMPRSS2-ERG gene re-arrangement events in aggressive prostate cancer [107]. MYC contributes to prostate cancer advancement by numerous potential ways, by directly stimulating cell growth through activation of ribosomal biogenesis, through transcriptional modulations of several oncogenic drivers like SOX4, EZH2 implicated in EMT and metastatic cascades, by mediating dysregulation of PI3K/AKT/MTOR signaling pathways to reprogram cell survival, through inhibition of essential tumor suppressors like NKX3.1 transcription factor and direct stimulation of replicative immortalization by means of overexpression of telomerase RNA TERC [105, 106, 108, 109]. Due to these multi-level involvement of prostate cancer pathogenesis, MYC is regarded as the highly desirable personalized therapeutic agent for future prostate cancer therapy [110]. Currently, an intense research is going on for development of several patient specific MYC targeting strategies such as inhibition of its transcription, disruption of its partner protein dimerization, suppression of its post-translational modification and checking its stabilities [106, 110].

6. Future strategic directions towards more effective therapeutic targeting in advanced prostate cancer

The future therapeutic strategy should accounts broad-spectrum mechanism based therapeutic targeting in advanced prostate cancer with a greater emphasis on patient specific drug target identification. Because the success of molecularly targeted therapy in complex disease like cancer mainly depends on precision in drug target set characterization during treatment of a particular patient

subgroup [111, 112]. The stark realities of these practical facts may be explained by observed lowest efficacies of anticancer drugs in comparison with other different diseases and unsatisfactory results obtained during the current clinical trialing of CRPCs with various therapeutic modalities, including immunotherapy [14, 16, 57, 58]. Current therapeutic approach neither addresses clinical complexities in castration resistance disease progression nor predicts any effective therapeutic target sets for maximizing the potential of multi-target attacking in CRPC. On the other hand, current research strongly supports for the existence of multiple alternative signaling circuitries driven by a number of oncogenes involved across a wide array of prostate cancer hallmark activities [8, 33, 73, 111]. For that reason, future broad spectrum approach should consider most of the critical factors that are principally responsible for current therapeutic unsuccessfulness observed among advanced prostate cancer patients. The factors are patient specific oncogenic activation events [84, 113], signaling complexities associated with CRPC progression & its bone metastatic propagation [76, 77], and the role of prostate cancer hallmarks [8, 111]. From this present scenarios, immunotherapeutic approaches in many cases may provide the desired effective avenues for targeting these multifactorial complexities through precise modulation of prostate tumor associated microenvironments [114–116]. In fact, the marked success of prostate cancer immunotherapy began in 2010 with FDA approval of Sipuleucel-T, a dendritic cell based autologous cellular vaccine for the personalized treatment of bone metastatic CRPC patients [114, 116]. Most importantly, it is increasingly believed that prostate tumor infiltrating immune modulatory cells like tumor associated macrophages (TAM), suppressor T cells (T_{REG}), myeloid derived suppressor cells (MDSC) and mesenchymal stem cells are centrally responsible for development of immunosuppressive tumor microenvironment, one of the potential barrier for attaining the required efficacies during immunotherapeutic treatments [114, 117, 118]. At the same time, these immunosuppressive cell populations are also significantly linked with prostate cancer advancement like its late phase of tumorigenesis, it's bone metastatic propagation and castration resistant disease progression [118–120]. For example, in a recent pre-clinical study reported in 2018 it has been found that androgen ablation therapy triggers the infiltration of IL-23 secreting MDSC's into the prostatic tissues of the mouse with a castration sensitive prostate cancer [121]. These secretion of IL-23 by MDSC's in turn critically drives the emergence of castration resistance through sustenance of AR receptor mediated signaling [121]. By administration of an anti-IL-23 antibody along with next generation antiandrogenic drug Enzalutamide essentially suppressed the genesis of castration resistance in corresponding mouse model. This somehow suggests that by targeting IL-23 pathway may help to increase the efficacies of Enzalutamide treatment [121, 122]. Numerous pre-clinical and clinical studies are currently involved for detail investigation of advanced prostate cancer targeting immunotherapeutic modalities over a diverse array of approaches including vaccine, immune checkpoint inhibitor (ICI), adoptive cell transfer (ACT), cytokines, immune modulators, virus induced immune modulatory effects and their various combinatorial formulations comprising at least one immune targeting agents [114, 123, 124]. A recent report indicates more than 1100 clinical trials are in progress for prostate cancer patients involving diverse therapeutic options, out of which 12% includes immunotherapeutic modalities [123]. But, to effectively apply these immunotherapies for patients of metastatic CRPC's, there also remains several potential challenges like the incidence of immunosuppression, immune-resistance and low levels of T cell infiltration in prostate tumor microenvironment (TME) [114, 116]. To critically focus on these major challenging areas, there is an urgency to get a comprehensive overview of prostate tumor associated immune interactions.

Principal attention in current prostate cancer research is mainly focused on characterization of its advanced disease features like castration resistance, bone metastasis and development of corresponding molecularly targeted therapeutics to tackle this frustrating situation [4, 6, 7, 76, 77]. But, in most of the cases current therapeutic strategy which is mainly based on targeting either androgen signaling pathways and cell proliferation wing or immune checkpoint blockade, cannot effectively cover the pathogenic complexities and signaling redundancies observed in CRPC [10, 16, 33]. Actually, the development of castration resistance state is markedly triggered by orchestration of several critical factors including AR dependent and independent pathways, interactions between AR signaling and alternative survival pathways, neuroendocrine trans-differentiation, prostate cancer stem cell, autophagy, tumor hypoxia, microenvironment, immune-suppression and selective pressure provided by ADT [8, 53, 53, 125]. Similarly, prostate cancer bone metastasis which adversely effects more than 90% of advanced prostate cancer patient is also an extremely pathologically complex phenomenon that is quite difficult to treat effectively with a single molecularly targeted agent like Denosumab or Zoledronic acid [126, 127]. This mechanistic complexities mainly arises due to persistence of complex reciprocal interactions between prostate tumor cell and bone microenvironment at multiple levels like prostate tumor-bone stromal cell (osteoblast & osteoclast), prostate tumor-bone matrix and tumor-vasculature interactions [76, 113, 128]. To effectively target these multifactorial complexities in advanced prostate cancer like situation, there is a real demand for elucidation of patient specific comprehensive mechanistic outlines of these corresponding pathological events [8, 80]. A patient centric real assessment of key cancer driver genes associated with prostate cancer cell growth, survival, proliferation, micro environmental contributions, immune-suppression and other critical factors like neuroendocrine trans-differentiation in castration resistance cases and vicious cycle in bone metastasis condition will provide right directions

towards personalized multi-target treatment selection in advanced prostate cancer patients [Table 3].

6.1 Broad-spectrum mechanism based strategic requirements for future personalized therapy in advanced prostate cancer

The vast experience gained from past researches on currently approved molecular targeted therapies and genome driven precision medicine approaches in prostate cancer explicitly reveals that prostate cancer is mostly heterogeneous in nature. An ultimate development of this heterogeneous disease is centrally fueled by an active participations of dysregulated androgen signaling and multiple cancer hallmarks activities [8, 111]. By considering this mechanistic point of view, current cancer research strongly recommends for identification of potential therapeutic combinations to further improve therapeutic efficacies in advanced prostate cancer [4, 114, 130–132]. For example, a large number of binary therapeutic combinations are currently involved for assessment of their effectiveness against CRPC patients in various phase I-III clinical trials [4, 6, 114, 130–133]. According to the recently reported information, in most of the cases the efficacies of such binary therapeutic combinations in point of overall survival remains questionable along with its toxicity burdens [4, 114, 130]. This therapeutic ineffectiveness of currently used binary therapeutic approaches may be explained by lack of systems level targeting in very complex disease like advanced prostate cancer. At the same time, it also opens a space for further development of broad-spectrum mechanism based therapeutic targeting in such conditions [132, 133]. In addition, current trends in molecular cancer therapeutics in many cases clearly reveals that by adopting an integrative strategy it may be possible in future to successfully address most of the so called major challenges in prostate cancer precision medicine like heterogeneity, toxicity, treatment resistance and its costing issues [33, 134, 135].

The concept of broad-spectrum hallmark based therapeutic targeting is deeply appealing in complex heterogeneous disease situations like advanced prostate cancer. The essentiality of this concept was proposed by "The Halifax Project", an international task force of biomedical researchers which provides the first basis of multi-target attacking framework in cancer [136, 137]. According to the guidelines proposed by "The Halifax Project", the broad-spectrum approach aims for identification of major cancer driver genes, its cancer hallmarks modulators, corresponding pathogenic pathways and mapping of host environmental factors known as "terrain factors". In the current investigation, by an extensive manual extraction of corresponding reports, we have identified 103 prostate cancer driver oncogenes, 8 prostate cancer associated features pathways and 5 metabolic "terrain factors", which explores the most probable spectrum of potential future therapeutic targets in context of prostate cancer advancement and its therapeutic recalcitrance [Tables 2 and 3]. Prostate cancer associated feature pathways are involved in several coordinated cell biological key processes that are centrally responsible for prostate cancer hallmarks manifestations to the acquisition of castration resistance like cell proliferation, cell death resistance, therapeutic resistance, bone metastatic propagation, cell to cell interaction, immune evasion and neuroendocrine differentiation. Metabolism associated "terrain factors" like inflammatory response, oxidation, glycemic condition along with stress induction also significantly contributes in a case dependent manner during prostate cancer progression and its subsequent metastatic development [Table 3]. These "terrain factors" may provide a very unique means to influence prostate cancer personalized treatment by providing an additional individualized complementary treatment approach through modulation of diet, exercise and life style patterns [136–138].

6.2 Future challenges in individualized combination therapy

As our understanding of prostate cancer disease mechanism and its therapeutic landscape is rapidly changing over time, there is a basic need to think for an integrative framework that will assist in patient specific identification of key prostate cancer driver proteins along with their effective therapeutic measures [84, 111, 132, 139]. By taking an in depth survey of currently available cancer therapeutic modalities, only combinatorial approaches seems to provide the right protection against an extremely complex multifactorial disease features like castration resistance and bone metastasis. This anticipation is due to two specific reasons, first future proposed therapy for CRPC will include simultaneous targeting of AR signaling axis, corresponding androgen independent signaling circuitries & major responsive hallmark activities. And the second one find an effective means to surpass therapeutic resistance events acquired during prostate cancer progression as a result of an intense interplay between prostate tumor heterogeneity, clonal evolution, immune-suppression and adaptive feedback loops operating within redundant signaling circuitries [16, 61, 81, 138, 140, 141]. Only individualized integrative approaches can provide the desired ambiance to successfully address these complex issues and most of the corresponding pre-clinical studies and current ongoing clinical trials on CRPC patients also conclusively supports these views that only a subset of metastatic CRPC patients shows significant improvement in overall survival along with a durable clinical response against a specific therapeutic combination [4, 8, 29, 57, 80, 114]. Current prostate cancer research reports for the development of numerous potential molecularly targeted therapeutic agents with a wide range of target spectrum including androgen signaling axis, oncogenic signaling pathway proteins, DNA damage repair associated proteins, transcription factors, epigenetic modulators and micro RNAs [4, 6]. A number of clinical trials are currently involved for detail evaluation of these proposed therapeutic agents in various combinatorial manner and some of which are still waiting for FDA approval. The future of personalized treatment for metastatic CRPC will significantly depends on patient specific development of synergistic combination of various immunotherapeutic approaches with the current conventional therapeutic means like androgen deprivation

therapy, chemotherapy, anti-androgens and radiation therapies [4, 80, 114]. Towards identification of patient specific optimal sequences for these future therapeutic measures, there is a growing requirement for identification of suitable biomarkers to guide effective treatment selection and characterization of treatment responses [24]. Recently, a number of genomic aberrations have been proposed as predictive biomarker for evaluation of treatment response profiles like cyclin-dependent kinase 12 (CDK12) and DNA damage repairs (DDR) associated breast cancer gene 1 (BRCA1) as well as ataxia telangiectasia mutated (ATM) in CRPC patients [142, 143]. It has been suggested that the biallelic loss of CDK12 are prevalent in around 5% of metastatic CRPCs and intrinsically associated with immunosuppression through massive infiltration of CD4 + FOXP3^{-} T lymphocytes in prostate TME, which strongly urges for the interventions with immunotherapeutic approaches [142]. On the other hand, it has been reported that nearly 11.8% of metastatic CRPCs have germ line alterations in DNA damage response associated mediators like BRAC1, BRCA2 and ATM, which are typically associated with the significant levels of response towards poly (adenosine diphosphate ribose) polymerase (PARP) inhibitor Olaparib [114, 143]. Based on recent TOPARP-A and TOPARP-B clinical trials among metastatic CRPC patients, PARP inhibitor Olaparib has been recommended as a personalized therapeutic agents in advanced prostate cancer for corresponding DDR defects accompanied by a marked enhancement in patients progression free survival (PFS) [20, 114, 142, 143]. Further strategic development of this kind of molecular stratification based treatment approaches for metastatic CRPCs will be of great demand in very near future with much accuracies.

7. Conclusions

The idea of prostate cancer precision medicine is highly promising but its desired application remains totally questionable in several major points. This is mainly due to several existing challenges which arises from different corresponding areas including heterogeneity, therapeutic resistance, signaling redundancies, biopsy related technical limitations, integration of multi omics data, lack of comprehensive mechanistic understanding and finally lack of overall knowledge of how to effectively combine present known drugs to significantly target patient specific key prostate cancer driver proteins. The current genome based precision medicine till now could not provide necessary directions to tackle these principal issues. Perhaps, it may be the holy grail of the entire cancer research field also which remains unexplained in point of clinical trial designing and its personalized focusing. In addition, there also exists other potential concerns like optimum sequencing strategies, efficacies of the currently available drugs and biomarker based patient's stratification. In fact, identification of patient subgroups according to their biomarker based assessment, subsequent effective treatment selection and proper evaluation of treatment response may provide the desired keys to personalize advanced prostate cancer treatment for individual patients. Furthermore, currently many leading experts suggests to avoid active treatment strategies like next generation anti-androgenic drugs in sequence for most of the metastatic CRPC patients. From this present situation, there is an acute urgency to find an alternative views for getting right directions in order to insightfully address all these major issues. This is the central aim of Prostate Cancer-Systems Medicine initiative which readdress the major postulates of "The Halifax Project" in context of prostate cancer precision medicine. At the same time this initiative also aims to focus on the basic groundwork required to construct the necessary future platform in prostate cancer precision medicine through identification of key molecular driver proteins involved in the process of prostate cancer oncogenesis, therapeutic resistance, disease progression as well as hallmark based clinical manifestation.

Currently a number of international task forces are involved to manage these challenging issues in prostate cancer and related research concerns. But, most of those task forces are mainly oriented in surgical, genomics and immunotherapy associated research activities which are not sufficient enough at any means to combat over present existing challenges in advanced prostate cancer. To successfully address these critical issues, Prostate Cancer Systems-Medicine Initiative essentially calls for the construction of common minimum platform by focused interactions among experts from diverse backgrounds. The present evaluation of corresponding facts and their underlying factors essentially recommends for the development of One Belt One Road approaches that will virtually connect each and every key issues and known concerned aspects of metastatic CRPCs towards an integrated framework which will assist in future patient specific therapeutic target set identification, their combination based targeting, prospective biomarker selection, and its proposed molecular classification based clinical trial designing in advanced prostate cancer.

Author contributions

DD coordinated all aspects of Prostate Cancer Systems-Medicine Initiative movement and its corresponding expert's interactions through an ongoing campaign from November, 2016 in Kolkata, India. MB, SB, TKM and BSS provided urologist's essential points. CB, AB and SK Das provided oncologist's view. SC added pathologist's opinion. PM, SS, LK and AB suggested pharmacologist's proposal. CKP, SR explained cancer biologist's facts. CB and SS provided physiologist's point of view. RK, NG, LN and KG gave data scientist's necessary opinion and support. AS revisited endocrinologist's principles. DD, MA and RK searched literatures, refined ideas and wrote manuscript with contributions from all authors. All authors approved basic theme, major statement and final conclusion.

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Conflict of interest

The authors declare no potential conflict of interest at any level.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at https://oss.jomh.org/jomh/article/1381518823473987584/attachment/Supplementary%20File.xlsx.

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