exhibit aerobic glycolysis and ^{18}F-FDG-PET has shown limited utility in PCa detection. Glycolytic features have been nevertheless reported in high-risk PCa, where the acquisition of a Warburg phenotype marks a more aggressive disease. Pertega-Gomes *et al.*[46] indeed observed a positive association between mRNA and protein levels of key glycolytic enzymes with worse clinicopathological features and biochemical recurrence (BCR). Accordingly, Choi and coworkers found high levels of lactate exporter monocarboxylate transporter 4 (MCT-4) protein in Gleason score (GS) 5 specimens, and again association with shorter time to develop BCR and CR[11]. Accordingly, high intraprostatic ^{18}F-FDG uptake in high-risk PCa patients was reported as an indicator of shorter BCR free survival and shorter time to CR following radical prostatectomy[47]. These data support the potential use of preoperative ^{18}F-FDG PET/CT as a non-invasive tool to distinguish patients in whom timely neo-adjuvant and adjuvant therapies should be explored.

The acquisition of a Warburg phenotype in mCRPC has been actively studied. Pertega-Gomes *et al*.[46] reported increased mRNA and protein expression of key glycolytic enzymes, including lactate dehydrogenase A (LDHA) and MCT-4 in mCRPC human specimens. Similar results were observed in the metastatic/CR TRAMP murine model by Bok and coworkers using hyperpolarized (HP) ^{13}C magnetic resonance spectroscopic imaging (MRSI) and multi-parametric ^{1}H magnetic resonance imaging (MRI)[48].

The first mechanistic explanation for a Warburg phenotype in the metastatic setting was provided by Diedrich and coworkers using a preclinical model of bone metastasis. According to the authors, bone marrow-enriched fat cells promote aerobic glycolysis in metastatic PCa cells via oxygen-independent HIF-1α activation and consequent induction of glycolytic enzymes[34]. While evidence for the same mechanism occurring in human mCRPC still need to be provided, these preliminary findings suggest a role for aerobic glycolysis in PCa progression/CR establishment and support the exploration of targeting LDHA and MCT transporters as new therapeutic opportunities for mCRPC, as discussed below.

Altogether, FA and glucose metabolism rewiring appears to be a recurrent feature associated with CR and resistance to ADT/AR signaling inhibitors, calling for the need of testing glycolysis and lipid metabolism modulators in combination with standard of care, as discussed below.

Aerobic glycolysis and neuroendocrine PCa

The role of aerobic glycolysis in neuroendocrine PCa (NEPC) has been the object of recent investigations. This very aggressive and lethal PCa subtype presents unique features, including loss of AR signaling during neuroendocrine transdifferentiation after treatment with AR-targeting anti-androgens, resulting in CR. Using patient-derived xenografts (PDXs), tumor tissues and gene expression data, Choi and coworkers reported enhanced glycolytic features associated with increased lactic acid production/secretion in NEPC. MCT-4 expression silencing in NEPC NCI-H660 cells was reported to inhibit cell proliferation, suggesting that elevated glycolysis coupled to excessive MCT4-mediated lactic acid secretion may be clinically relevant to NEPC. Consequently, targeting MCT4 might be worth testing as a new therapeutic strategy for NEPC[49]. Discordant results were, however, reported by Zacharias *et al.*[50] using *in vivo* HP MRSI, as well as lactate measurements *ex vivo*. The authors reported increased lactate production in AR-dependent CRPC PDX models compared to AR-negative neuroendocrine PDX models, highlighting the need for further experimental work to fully elucidate the role of aerobic glycolysis in NEPC and the clinical potential of therapeutic approaches that target it.

Metabolic alterations beyond lipid and glucose metabolism and castration resistance

The advent of metabolomics technologies has allowed for the unbiased interrogation of cancer metabolism and the identification of metabolic pathways involved in CR, previously uncharacterized. In 2013, the group led by Chinnaiyan used high-throughput liquid and gas chromatography-based MS (LC/GC-MS) to profile the metabolome of 262 clinical samples (42 tissues, including 14 metastatic tissues, and 110 each

of urine and plasma). Metabolic profiling was able to distinguish clinically localized PCa from mCRPC. Importantly, sarcosine, an N-methyl derivative of the amino acid glycine, emerged as a differential metabolite highly increased in mCRPC, and detectable non-invasively in urine. The authors went further to demonstrate AR binding to the promoter of the gene of glycine N-methyltransferase, the enzyme that coverts glycine into sarcosine, suggesting an interplay between AR and the sarcosine pathway[51]. Unfortunately, other studies did not confirm sarcosine as a biomarker for aggressive PCa, most likely due to the technical difficulties to accurately measure sarcosine, and the difference in the study population[52]. Thus, improvements in sarcosine detection and a careful design of prospective studies are still strongly needed before this biomarker can be used in precision medicine.

Following this first study, several groups have investigated the metabolic changes that support CR acquisition. In 2014, Kaushik and coworkers used a combination of targeted MS and metabolic phenotyping and identified nineteen metabolites that were altered in androgen-independent compared to androgen-dependent cell lines. These altered metabolites mapped to a highly interconnected network of biochemical pathways that describe UDP glucuronosyltransferase activity and were associated with time to treatment failure[53]. The year after, Shafi and al. reported an increase in glutaminolysis and reductive carboxylation in CRPC cell lines harboring AR-V7, suggesting their potential involvement in the resistance to endocrine therapies[54]. More recently, the group of Freedland combined metabolomics and lipidomics in patient serum and identified reduction in steroid synthesis, ketogenesis and hyperglycemia as prominent hallmarks of ADT treatment, suggesting the potential use of restricted ketogenic diets in improving ADT-linked comorbidities[55]. Altogether, these findings support a scenario where metabolic pathways other than FA and glucose metabolism may be altered in CRPC, suggesting the involvement of a more complex metabolic network in the acquisition of CR.

GENETIC DRIVERS, METABOLIC REPROGRAMMING, AND RESISTANCE TO ANDROGEN THERAPIES

Genomic analyses showed the molecular heterogeneity of mCRPC. The most common alterations are AR amplifications/mutations (63%), p53 loss (53%) PTEN loss (50%), MYC amplification (18%), PI3K mutations (< 15%), BRAC1 and BRAC2 mutations (14.6%)[56]. All these genetic alterations have been associated with resistance to endocrine therapies through different mechanisms, including metabolism reprogramming, highlighting the tight link between genetic drivers, metabolic alterations and CR. CR following PTEN loss has been associated with alterations in the metabolic flux of glycolysis, glutaminolysis, branched-chain amino acid catabolism and FA metabolism[57]. The latter has gained special attention since Chen *et al*.[58] demonstrated that co-deletion of PTEN and promyelocytic leukemia protein (PML) activates mitogen-activated protein kinase, resulting in a SREBP-dependent lipogenic program that promotes mCRPC. Concordantly, HFD triggered SREBP-dependent lipogenesis and induced metastasis in the nonmetastatic PTEN knockout (KO) model and further enhanced metastasis in the PTEN/PML KO model, suggesting the lipogenic program as an underlying rheostat toward metastatic PCa progression. More recently, PTEN loss has been associated with CR via intratumoral androgen synthesis triggered by the KT-RUNX2-OCN-GPRC6A-CREB signaling axis, resulting in the overexpression of the *CYP11A1* and *CYP17A1* genes[59].

The oncogene c-MYC (hereafter called MYC) is a well characterized master metabolic regulator. MYC controls a wide range of metabolic pathways, including glycolysis, glutaminolysis, FA metabolism (both synthesis and oxidation) and protein synthesis[60,61]. MYC is overexpressed early in the disease and amplified in about 20% of mCRPC, and its transcript levels are increased in AR-V7-high bone metastases[56,62,63]. MYC is an androgen-independent, AR-dependent targeted gene, whose protein overexpression induces androgen-independent PCa growth in preclinical models[64]. Recently, two studies showed MYC

involvement in AR-V7 stabilization and in the regulation of alternative splicing, linking MYC with the acquisition of resistance to endocrine therapies[65,66]. In 2015, Mills and coworkers demonstrated MYC regulation of phosphoribosylaminoimidazole carboxylase (PAICS) and inosine monophosphate dehydrogenase 2 (IMPDH2), enzymes involved in *de novo* purine biosynthesis. High expression levels of the *PAICS* and *IMPDH2* genes were reported in mCRPC, while IMPDH2 inhibition with mycophenolic acid sensitized the response to AR signaling inhibitors, suggesting a potential role for PAICS and IMPDH2 in mediating the resistance to endocrine therapies[67].

p53 is a tumor suppressor able to revert many of the metabolic effects exerted by MYC through inhibition of genes associated with glucose uptake, pentose phosphate shunt and nucleotide synthesis pathway[68,69]. p53 was reported to directly bind to the promoter region of SREBP-1, inducing gene silencing and *de novo* lipogenesis inhibition[70]. p53 inactivation was also associated with alterations in glucose, FA, oxidative phosphorylation, glutathione metabolism[71] and inhibition of AR activity[72]. In 2018, Maughan and coworkers showed that p53 status in the primary PCa is predictive of inferior response to AR signaling inhibitors in mCRPC[73], suggesting that p53 loss-associated metabolic alterations might be involved in the acquisition of resistance to AR signaling inhibitors.

PCa patients carrying BRCA 2 mutations become resistant to ADT faster than non-carriers[74]. Whether BRCA 2 mutation status affects the response to AR signaling inhibitors is still an object of investigation[75]. It has been reported that breast cancers harboring BRCA 1 mutations manifest a Warburg-like phenotype[76], which might also characterize BRCA 2-mutated mCRPC. Future investigations are required to explore this aspect.

TARGETING METABOLIC VULNERABILITIES TO OVERCOME RESISTANCE TO ENDOCRINE THERAPIES

Inhibitors of de novo fatty acid and cholesterol synthesis

As lipid metabolism rewiring, in the form of increased FA and cholesterol synthesis, uptake and oxidation, is a hallmark of mCRPC and resistance to endocrine therapies, efforts have focused on tackling enzymes and transporters involved in these processes.

FASN, the key enzyme in the synthesis of FA palmitate, is certainly the most studied and the best characterized therapeutic target. However, despite the positive results in the preclinical setting, off-target effects, poor solubility and pharmacokinetics, and untoward side effects, including important weight loss, have hampered the clinical translation[77]. This reality has recently changed with the development of TVB-2640, an orally available inhibitor of the FASN β-ketoacyl reductase domain. A phase I clinical trial has been recently completed proving the safety and efficacy of the drug in patients with advanced solid malignancies (NCT02223247). Combined with paclitaxel, TVB-2640 proved to be beneficial in heavily pretreated breast cancer patients, while the non-orally available analog TVB-3166 has shown promising results in preclinical models of mCRPC[78-80]. Phase II trials are now investigating TVB-2640 in several solid tumor types (NCT03032484, NCT03179904, NCT02980029 and NCT03808558) [Table 1].

In the context of mCRPC, our group characterized a new small-molecule FASN inhibitor (IPI-9119) and demonstrated that selective FASN inhibition antagonizes the growth of mCRPC in *in vitro* models through metabolic reprogramming and results in reduced protein expression and transcriptional activity of both AR-FL and AR-V7. Interestingly, FASN inhibition in mCRPC cells harboring AR-V7 downregulated especially the variant, suggesting a distinctive interplay between AR-V7 and *de novo* lipogenesis. Mechanistically, FASN inhibition triggered the activation of the endoplasmic reticulum stress response, resulting in reduced protein synthesis. Our analysis also demonstrated consistent inhibition of MYC and

Table 1. Promising metabolic drugs currently explored for the treatment of CRPC in combination with ADT, AR signaling inhibitors, or chemotherapy

Drug	Metabolic Target	Model	Anti-cancer effect	Drugs combination	Drug development timeline
Lipid metabolism					
TVB-3166	FASN	- mCRPC human cell lines - mCRPC xenografts	mCRPC cell lines - Reduction of AR/AR-V7 proteins - Reduction of proliferation/soft agar colony growth - Induction of apoptosis - Reduction of oncogenic signaling (i.e., b-catenin, c-MYC, *etc.*) CRPC xenografts - Reduction of xenograft tumor growth	TVB-3166+ paclitaxel - FASN inhibition-mediated increase of taxanes efficacy in CRPC	Preclinical - The orally available, TVB-2640 is currently tested in patients with various cancer types (Phase 2 trials: NCT03032484, NCT03179904, NCT02980029, NCT03808558)
IPI-9119	FASN	- mCRPC cell lines - mCRPC xenografts - Human mCRPC organoids	Androgen sensitive and mCRPC cell lines - Reduction of AR/AR-V7 proteins - Reduction of proliferation/soft agar colony growth - Cell cycle inhibition - Induction of apoptosis - Induction of endoplasmic reticulum (ER) stress - Reduction of protein synthesis mCRPC xenografts - Reduction of xenograft tumor growth Human mCRPC organoids - Reduction of mCRPC organoid growth	IPI-9119+ enzalutamide mCRPC cell lines - FASN inhibition-mediated increase of enzalutamide efficacy in mCRPC cells	Preclinical
Atorvastatin	HMGCR	Humans	NA. Recruiting stage. Primary objective - This randomized double-blind placebo-controlled trial is designed to explore whether the intervention with atorvastatin delays PCa progression (i.e., development of CR compared to placebo during ADT for metastatic or recurrent PCa)	Atorvastatin+ADT	Phase 3 trial (NCT04026230)
Mevastatin Simvastatin	HMGCR	- mCRPC cell lines - mCRPC xenografts	mCRPC cell lines - Reduction of AR/AR-Vs proteins via inhibition of mTOR pathway - Reduction of proliferation - Induction of apoptosis - Reduction of p-mTOR, p-Akt, p-S6RP mCRPC xenografts - Reduction of xenograft tumor growth - Reduction of proliferative rate - Increase of apoptotic rate	Simvastatin+enzalutamide mCRPC xenografts - Simvastatin-mediated increase of enzalutamide efficacy in mCRPC - Higher reduction of proliferative rate in the combo - Higher increase of apoptotic rate in the combo	Preclinical
BMS-303141	ACLY	- mCRPC cell lines - mCRPC xenografts	mCRPC cell lines - Reduction of proliferation - Reduction of AR protein - Induction of apoptosis - Activation of AMPK - Induction of ER stress	BMS-303141+enzalutamide - BMS-303141-mediated increase of enzalutamide efficacy in mCRPC via AMPK activation - Dramatic suppression of AR and AR target gene expression - Higher reduction of proliferative rate in the combo - Higher increase of apoptotic rate in the combo - Stronger induction of ER stress in the combo	Preclinical
Etomoxir	CPT-1	- mCRPC cell lines	- Reduction of proliferation/soft agar colony growth	Etomoxir+Enzalutamide - Etomoxir-mediated increase of Enzalutamide efficacy in mCRPC cells - Higher reduction of proliferative rate/ soft agar growth in the combo	Preclinical - The clinical translation of Etomoxir has been terminated due to its toxic side effects

Ranolazine	3-KAT*	- mCRPC cell lines - mCRPC xenografts	mCRPC cell lines - Reduction of proliferation/soft agar colony growth	Ranolazine+enzalutamide mCRPC cell lines - Ranolazine-mediated increase of enzalutamide efficacy in mCRPC cells - Higher reduction of proliferative rate/ soft agar growth in the combo mCRPC xenografts - Higher reduction of proliferative rate in the combo	Preclinical #
Perhexilline	CPT-1	- mCRPC cell lines	- Reduction of proliferation/soft agar colony growth	Perhexilline+enzalutamide - Perhexilline-mediated increase of enzalutamide efficacy - Higher reduction of proliferative rate/ soft agar growth in the combo	Preclinical #
Glucose metabolism					
AR-C155858	MCT-1	- *Ex-vivo* tissue slices of human PCas	- Reduction of proliferative rate - Increase of apoptotic rate		Preclinical - AstraZeneca MCT-1 inhibitor (AZD3965) is currently tested in patients with advanced solid tumors (Phase I trial: NCT01791595)
FX11	LDHA	- ATM-deficient mCRPC cells - ATM-deficient mCRPC xenografts	ATM-deficient mCRPC cell lines - Reduction of viability rate - Increase of ROS levels ATM-deficient mCRPC xenograft - Reduction of tumor growth in FX11-treated group		Preclinical
Gossypol (AT-101)	LDHA	- Humans	Study No. 1: Test of AT-101 and ADT in patients with newly diagnosed metastatic PCa Study No. 2: Comparison of AT-101 with docetaxel and prednisone *vs.* docetaxel and prednisone alone in men with chemotherapy-naïve metastatic hormone refractory PCa (HRPC) Study No. 3: Test of AT-101 in men with HRPC Study No. 4: Test the safety and efficacy of AT-101 in combination with docetaxel and prednisone in men with HRPC	Primary objectives: Study No. 1: Determine the % of patients with newly diagnosed metastatic PCa with undetectable PSA (< 0.2 ng/mL) at 7 months following treatment with AT-101 and ADT Study No. 2: Compare the two treatment arms with respect to overall survival (time frame: 33 months) Study No. 3. Determine the number of participants treated with AT-101 showing adverse events Study No. 4: Determine the safety of AT-101 in combination with docetaxel and prednisone (time frame: 12 months)	Study No. 1: Phase 2 trial: NCT00666666 Study No. 2: Phase 2 trial: NCT00571675 Study No. 3: Phases 1/2 trial: NCT00286806 Study No. 4: Phases 1/2 trial: NCT00286793

*3-KAT: 3-ketoacylthiolase; [#]These drugs are already approved in Europe, US, and Australia for the treatment of heart diseases in patients

the MYC-mediated transcriptional program, following FASN suppression. As mentioned above, MYC promotes CR and AR-V7 stabilization and competes with AR for binding to AR-regulated genes. Thus, the opportunity to repress AR/AR-V7 and MYC signaling simultaneously is particularly attractive in the mCRPC setting. *In vivo*, IPI-9119 reduced the growth of AR-V7-driven mCRPC xenografts and human mCRPC-derived organoids. IPI-9119 and enzalutamide combination induced higher mCRPC cell growth

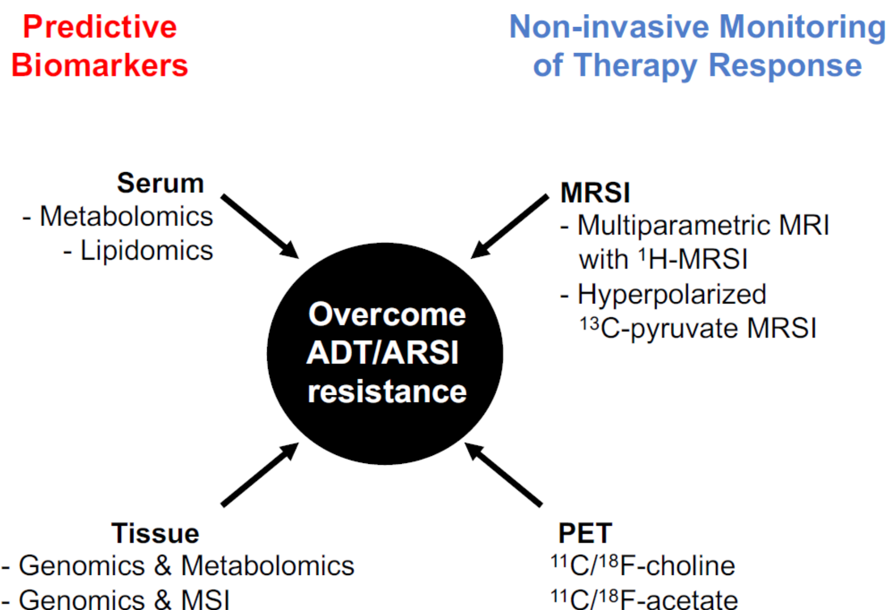

Figure 3. Metabolomics and metabolic imaging applications in PCa. Schematic overview of metabolomics and metabolic imaging applications in biomarker discovery and in therapy response assessment. ADT: androgen deprivation therapy; ARSI: androgen receptor signaling inhibitors; MSI: mass spectrometry imaging; MRI: magnetic resonance imaging; MRSI: magnetic resonance spectroscopy imaging; PET: positron emission tomography

of metabolomics, an issue that has prevented the use of metabolic biomarkers in the clinical routine so far. Moreover, pre-analytical and technical obstacles, statistical artifacts and confounding factors are still unresolved issues. Carefully designed future studies with appropriate sample size, controls in place at the pre-analytical, analytical, and clinical stage, and finding validation using an appropriate set of independent samples are absolutely required prior the integration of metabolomics in the practice of precision medicine.

Despite the crucial role of lipid metabolism in PCa progression and resistance to endocrine therapies, lipidomics studies have only recently been reported in the literature, most likely due to the methodological challenge of analyzing simultaneously diverse lipid classes and molecular species. However, these studies are now becoming increasingly popular in the field of biomarker discovery. Lin *et al.*[105] performed LC/MS-based lipidomic profiling on plasma samples from a discovery cohort of CRPC patients and validated the results in an independent cohort. Unsupervised analysis of lipidomic profiles classified the discovery cohort into two subgroups with significant survival differences (HR = 2.31; 95%CI: 1.44-3.68; P = 0.0005). Forty-six lipids, predominantly sphingolipids, were associated with poor prognosis. The authors were able to derive and validate a prognostic three-lipid signature (ceramide d18:1/24:1, sphingomyelin d18:2/16:0 and phosphatidylcholine 16:0/16:0) as independent prognostic factor[105]. Moreover, the group of Butler used lipidomics to profile PCa cell lines, xenografts and patient-derived explants under treatment with androgen and AR signaling inhibitors. The authors identified changes in lipid elongation for multiple phospholipid classes in response to androgen treatment, which was reversed by enzalutamide, suggesting the utility of lipidomics to predict response to endocrine therapies[83].

While the high resolution, sensitivity and specificity of LC/MS-based metabolomics and lipidomics have favored their use in biomarker discovery, these technologies, which analyze metabolite extracts, fail to provide spatial information, preventing the possibility to interrogate cancer biomarkers in relation to tissue pathology and compartment distribution. The development of MSI has overcome this limitation, allowing the overlap of metabolic and pathology information on the same tissue section. MSI thus represents an important step forward for the evaluation of metabolic reprogramming occurring in the TME. Matrix-

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