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Review

# Prostate cancer-specific hallmarks of amino acids metabolism: Towards a paradigm of precision medicine

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ABSTRACT

So far multiple differences in prostate cancer-specific amino acids metabolism have been discovered. Moreover, attempts to utilize these alterations for prostate cancer diagnosis and treatment have been made. The prostate cancer metabolism and biosynthesis of amino acids are particularly focused on anaplerosis more than on energy production. Other crucial requirements on amino acids pool come from the serine, one-carbon cycle, glycine synthesis pathway and folate metabolism forming major sources of interproducts for synthesis of nucleobases necessary for rapidly proliferating cells. Considering the lack of some amino acids biosynthetic pathways and/or their extraordinary importance for prostate cancer cells, there is a widespread potential for targeted therapeutic applications with no effect on non-malignant cells. This review summarizes the up-to-date knowledge of the importance of amino acids for prostate cancer pathogenesis with a special emphasis on potential applications of metabolic variabilities in the new oncologic paradigm of precision medicine.

## 1. Introduction

Cancer cells manifest metabolic alterations that distinguish them from cells in normal tissues, and make them vulnerable to anticancer agents. From the extensive spectrum of such alterations, a number of differences in metabolism, biosynthesis and content of both proteinogenic and non-proteinogenic amino acids have been found highly abundant in prostate cancer (PCa). These metabolic alterations support the ability of PCa cells to survive the in unfavourable conditions, such as hypoxia, oxidative stress and to feed high energetic demands.

Due to a frequent molecular heterogeneity and clinical variability, PCa can manifest as a benign growth that can be safely watched or as aggressive malignancy that can prove fatal [1]. Such variability results in multiple forms of PCa that differ in onset age, aggressiveness, metastatic potential, hormonal responses, and also markedly complicates the diagnostic/prognostic and therapeutic accuracy [2]. The first-line PCa screening tool combines a digital rectal examination and quantitation of serum prostate specific antigen (PSA). This increases the detection rates and awareness of PCa; however, still false-positive/negative results are common, as well as poor discriminative ability of aggressive forms of PCa [3]. Therefore, biomarkers able to detect the early stages of PCa are still of utmost interest. It is worth to note that some of them (alpha methylacyl-CoA racemase, *TMPRSS2-ERG* fusion, caveolin-1, annexin-3, circulating RNAs, small metabolites, such as 8-hydroxy-2′-deoxyguanosine or amino acids) have provided promising data, and thus their benefit for PCa screening is still extensively investigated [3–8]. In case of the positive results, follow-up examination includes transrectal ultrasonography and magnetic resonance imaging that often enable for a guidance of the only test that can fully confirm and classify PCa – biopsy followed by a histopathology examination. Moreover, emission/computed tomography and bone scans are utilized to detect lymph node and bone metastases [2,9].

The primary approach for the treatment of PCa metastases comprises androgen ablation using gonadotropin-releasing hormone analogues (zoladex, casodex, *etc.*) or antiandrogens (enzalutamid) [10]. Moreover, to prevent skeletal complications, men with bone metastases are often treat with zoledronate or denosumab [11]. Men who do not respond to hormone therapy often undergo chemo- or immunotherapy. As a standard chemotherapy, docetaxel and cabazitaxel can be used and are often combined with prednisone [12]. The most recent treatment

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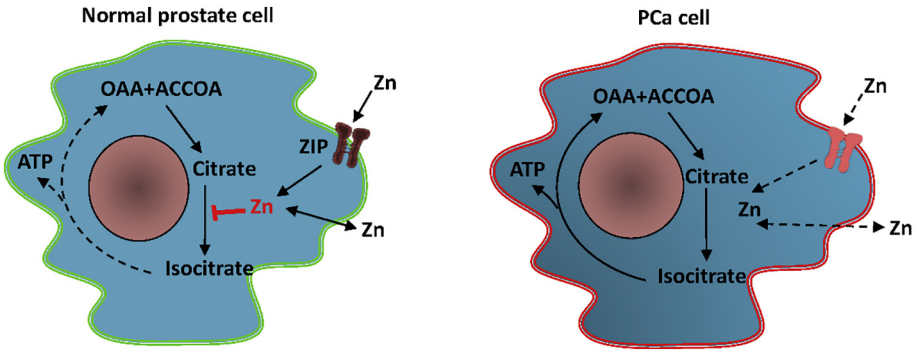


**Fig. 1.** The importance of Zn in prostate cells. In healthy cells, zinc transporters (ZIPs) enables for extensive Zn accumulation, which results in inhibition of citrate oxidation and respiration. Contrary to that, PCa cells exhibit genetic transformations (frequently epigenetic) that silence ZIPs and inhibit accumulation of Zn. As a result, the Krebs cycle become functional and ATP production is increased making the PCa cells bioenergetically efficient.

option utilizes the patient's own immune system to identify and destroy PCa metastatic cells. For this purpose, sipuleucel-T is tailored autologously by patient's dendritic cells extracted by leukapheresis [13]. The dendritic cells are subsequently incubated with the recombinant protein PA2024 that activates dendritic cells and helps them to mature. Despite that, it must be noted that virtually no treatments can efficiently cure advanced/metastatic PCa, and the discussed approaches are particularly effective in prolonging the patient's life and control the symptoms. Hence, the detailed understanding of PCa-specific metabolic alterations might lead to a development of novel diagnostic and therapeutic tools required to improve PCa management.

One of the most notorious characteristics of PCa cells is a marked decrease in zinc and citrate (Fig. 1). In normal prostatic gland, compared to other soft tissues, 3–10-fold higher amount of zinc is accumulated within a peripheral zone inevitably causing inhibition of *m*-aconitase that can catalyze the stereo-specific isomerization of citrate to isocitrate. This phenomenon results in accumulation and secretion of citrate that is vital intermediate in the tricarboxylic acid (TCA) cycle. The loss of zinc accumulation during PCa progression results in a pronounced oxidation of citrate and stimulation of TCA cycle, thus making the cells more energy-efficient. Moreover, the stimulatory effect is magnified by elimination of apoptogenic influence of zinc [14].

Therefore, unlike other solid tumors, the metabolism and biosynthesis of amino acids in PCa is focused particularly on anaplerosis more than on energy production. Another crucial requirement on amino acid metabolism comes from the serine, one-carbon cycle, glycine (SOG) synthesis pathway and folate metabolism providing pools of interproducts for synthesis of nucleobases necessary for rapidly proliferating cells [15]. These facts underpin the potential of specific amino acids deprivation in PCa therapy [16]. At the level of gene expression, SOG pathway is up-regulated in up to 9% of PCa cases. Noteworthy, it was shown that expression of *Myc*, its down-stream targets, as well as *TMPRSS2-ERG* fusion and Gleason score positively correlate with the SOG pathway signature in PCa cells [15]. Several potentially useful deviations in amino acid patterns have been found between malignant *vs.* non-malignant PCa cell lines and also in urine of PCa patients [17–19].

Hence, the aim of this review is to summarize the up-to-date knowledge about the role of amino acids and their metabolical pathways in PCa pathogenesis. Moreover, potential applicability of these biochemical processes for PCa diagnosis, classification and therapy is discussed as well. The overview of the importance of amino acids in PCa pathogenesis and possible utilization of their associated pathways for PCa therapy is summarized in Table 1. On the following pages, three-letter abbreviations (together with systematic IUPAC names) for proteinogenic and well-established abbreviations for non-proteinogenic amino acids are utilized.

## 2. Glycine (Gly, aminoethanoic acid)

Despite its simple structure and high abundance, Gly has been found to significantly correlate with proliferation rates across distinct NCI-60 cancer cell lines. Gly conversion significantly contributes to the biosynthetic requirements of purines, adenosine triphosphate (ATP) and reduced nicotinamide adenine dinucleotide phosphate (NADPH), which are necessary for cancer cells proliferation. Furthermore, Gly metabolism is tightly interconnected with metabolism of serine (Ser) as discussed below. Alterations in Gly metabolism that result in elevated Gly pool and altered ratios to other amino acids are therefore considered as plausible predictors of metastatic PCa [38].

### 2.1. Gly biosynthesis and metabolism of tetrahydrofolate (THF)

Deregulation of mitochondrial biosynthetic pathway of Gly, together with up-regulation of mitochondrial folate enzymes has been observed in numerous cancer cell lines [45]. Intracellular synthesis of Gly is compartmentalized between the cytosol and mitochondria, providing two separate enzymatic pathways (Fig. 2). It is worth to note that the rate of proliferation of prostate cells was found to directly correlate with up-regulation of mitochondrial part of enzymes involved in Gly metabolism, namely serine hydroxymethyl transferase (SHMT2), methylene-THF dehydrogenase (MTHFD2), and THF-synthetase.

Interestingly, in the same experimental setup, the expression of cytosolic enzymes was not altered, highlighting the key role of mitochondria in cancer cells proliferation [45]. It should be noted that approx. 10% of PCa cases manifest a significant up-regulation of the folate metabolism gene signature [20], indicating them as plausible biomarkers for PCa classification. From therapeutic point of view, PCa cells have been found highly sensitive to folate manipulation. For instance, Bistulfi and coworkers identified that even mild dietary folate depletion arrested PCa progression in TRAMP mice [21]. These entire facts highlight that combinational therapy utilizing antifolates paired to approved anticancer agents might lead to marked improvement of PCa therapeutic efficiency. In 1996, Sagaster et al. conducted a randomized prospective clinical trial using combination of maximal androgen blockade (MAB, orchiectomy followed by Flutamide therapy) with Methotrexate (MTX) [46]. Despite only non-significant gains in remission rates (42.3% MAB + MTX *vs.* 29.6% MAB) were achieved, further investigation of combinations of antifolates with approved cytostatic drugs possessing distinct mechanisms of actions might result in improvement of outcomes of PCa therapy.

### 2.2. Enzymes driving metabolism of Ser/Gly

The ectopic expression of enzymes driving Ser and Gly catabolism, namely phosphoserine aminotransferase (PSAT) and SHMT is capable to induce prostate tumor formation *in vivo* [25]. Interestingly, this phenomenon was closely dependent on enhanced activity of glycine decarboxylase (GLDC). Taken together, this phenomenon explains the fact, that an increased availability of Gly or sarcosine (Sar) results in an enhanced invasiveness of PCa cells [38], and that Gly uptake and catabolism have marked stimulatory effects on prostate tumorigenesis and

**Table 1**
Overview of the roles of amino acids in a pathogenesis of PCa.

| Amino acid | Importance for PCa cells | Possible linkage to PCa therapy | Ref. |
|---|---|---|---|
| Glycine (Gly, G) | Deregulation of mitochondrial biosynthesis<br>Up-regulation of THF metabolism<br>Ser/Gly metabolism | Folate depletion, Antifolates<br>DNA demethylating agents, bases analogs<br>Ser/Gly starvation | [20,21] |
| Glutamine (Gln, Q) | Production of fatty acids and nucleotides precursors in TCA cycle (α-ketoglutarate)<br>Glutaminolysis | Carbohydrate and Gln restriction | [22,23,24] |
| Serine (Ser, S) | Increased biosynthesis<br>SOG pathway<br>Shifting from OXPHOS to glycolysis<br>Zinc metabolism | PHGDH targeting<br>Antifolates<br>PKM2 targeting | [15,25,26] |
| Proline (Pro, P) | Apoptotic signaling<br>ROS scavenging<br>Pyridines precursors | PRODH inhibitors | [27,28] |
| Arginine (Arg, R) | Up-regulation of Arg metabolism | NOS or arginase targeting<br>Arg deprivation | [29,30] |
| Leucine (Leu, L) | LATs up-regulation<br>Activation of mTOR signaling by Leu | Leu analogues for LATs targeting | [31,32] |
| Methionine (Met, M) | Crucial for protein synthesis, chromatin and protein methylation<br>GSH synthesis<br>Hcy is not used as Met precursor | Met restriction<br>Urinary marker of PCa progression | [33,34] [35] |
| Tryptophan (Trp, W) | Serotonin precursor<br>Immunoregulation | IDO targeting to prevent Trp degradation | [36,37] |
| Sarcosine (Sar) | PCa proliferation and invasiveness<br>Intermediate in Gly synthesis<br>Connected with others metabolism of Met, Ser, Gly | Sar detection for PCa sub-classification | [17,38,39] |
| Hydroxyproline (Hyp) | Precursor of Gly, pyruvate and glucose<br>ROS scavenger | Urinary marker of PCa bone metastases | [40,41] |
| Taurine (Tau) | Decreases expression of PSA and metastasis-related proteins<br>Attenuates EMT-related genes<br>Putative signaling molecule | Tau and *N*-acyl Tau treatment decreases cell proliferation and neoplasticity | [42,43,44] |

THF, tetrahydrofolate; TCA, tricarboxylic acid; PHGDH, phosphoglycerate dehydrogenase; SOG, serine, one-carbon cycle, glycine; PKM2, pyruvate kinase 2; ROS, reactive oxygen species; PRODH, proline dehydrogenase; NOS, nitric oxide synthase; LATs, *L*-type amino acid transporters; mTOR, mammalian target of rapamycin; GSH, reduced glutathione; Hcy, homocysteine; IDO, indoleamine 2,3-dioxygenase; EMT, epithelial-mesenchymal transition.

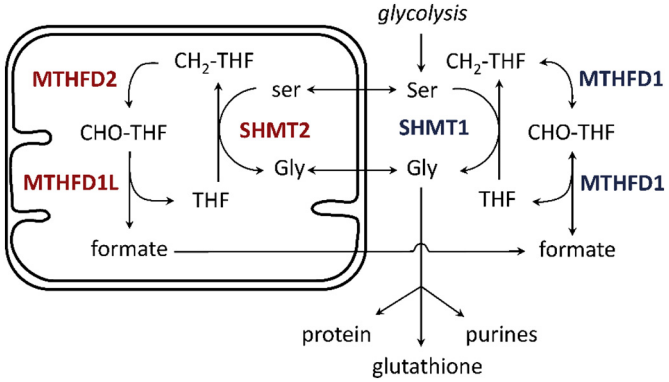


**Fig. 2.** Schematic drawing of cytosolic and mitochondrial Gly metabolism. Red – mitochondrial enzymes, blue, cytosolic enzymes. MTHFD2 – Bifunctional methylenetetrahydrofolate dehydrogenase/cyclohydrolase, mitochondrial, MTHFD1L – Monofunctional C1-tetrahydrofolate synthase, mitochondrial, SHMT2 – Serine hydroxymethyltransferase 2, SHMT1 – Serine hydroxymethyltransferase 1, MTHFD1 – C-1-tetrahydrofolate synthase, cytoplasmic, THF – tetrahydrofolate, CHO-THF – 10-formyl-tetrahydrofolate, CH2-THF – 5,10-methylenetetrahydrofolate. Adapted and modified according to Jain et al. [45]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

malignancy [25].

Another substantial example of importance of Ser/Gly metabolism enzymes was evidenced in our previous study, demonstrating that upon Gly exposure, expression of Sar metabolism-related enzyme glycine *N*-methyltransferase (GNMT) was up-regulated in metastatic PCa cells (PC-3) and primary tumor cells (22Rv1), but not in cells derived from normal prostate epithelium (PNT1A) [17]. During this process, elevated intracellular Sar is formed from Gly by adding a methyl group from a major methyl donor *S*-adenosylmethionine (SAM), thus regulating intracellular methylation processes whose disequilibrium is considered the major hallmark of cancer development and progression [47]. These findings open new avenues for testing the DNA demethylating agents in PCa therapy. Some promising preclinical *in vitro* and *in vivo* studies have already been achieved using Disulfiram [48] or Decitabine [49]. In 2007, a phase I/II study revealed that Azacitidine can reverse clinical resistance of metastatic PCa to Docetaxel through epigenetic deregulation [50]. One can speculate about the possible efficiency of Gly deprivation as auxiliary tool during PCa therapy. Indeed, several studies revealed that dietary Gly and Ser starvation can reduce tumor growth in xenograft and allograft models [51–53]. Notably, K-ras-driven cancers were less responsive to Ser/Gly starvation, suggesting an importance of K-ras in regulation of expression of enzymes involved in Ser/Gly metabolism [54].

## 3. Glutamine (Gln, 2-amino-4-carbamoylbutanoic acid)

Gln is a non-essential proteinogenic amino acid playing a central role in the metabolism of majority of amino acids. Gln comprises up to 60% of the total free amino acids in blood plasma. Despite its classification, Gln shows to be conditionally essential under some physiological conditions, particularly due to its involvement in several metabolic pathways and cell signaling. Moreover, Gln acts as nitrogen donor for purine and pyrimidine nucleotide synthesis, synthesis of other amino acids, carbamoylphosphates, amino sugars and other metabolites crucial for cellular proliferation. In addition, especially in cancer cells, Gln serves as carbon donor and an energy source for a broad number of cellular processes [55].

### 3.1. Regulation of Gln metabolism and importance of glutaminolysis

In cancers, glutamic acid (Glu) metabolism is tightly regulated by several factors, such as MYC, p53, Ras and HIF. This modulation is maintaining cancer growth, and is one of the important inducers of carcinogenesis [22].

During this process, Gln is converted to glutamic acid (Glu), constituting the first step of glutaminolysis. Glu is then transformed to α-ketoglutarate that enters to TCA producing citrate and malate for synthesis of fatty acids and nucleotides [56]. In solid tumors lacking glucose, glutaminolysis is of inevitable importance. In PCa, mutations in mitochondrial DNA are frequent and result in impairment of TCA cycle and/or OXPHOS, forcing the cancer cells to use alternative pathways [23]. This process can be mechanistically influenced by a number of oncogenes, including *MYC*, *AR* or *mTOR* that converge to increase Gln uptake in PCa through elevating expression of distinct Gln transporters (SLC1A4, SLC1A5, *etc.*) [57]. These data highlight that oncogenic drivers have a pronounced impact on a promotion of Gln uptake and its metabolism, which underpins Gln importance for proliferation of PCa cells. Indeed, in a recent study by Zacharias et al. it was described that highly aggressive, metastatic subline of PC-3 cells markedly increases Gln utilization [58], supporting the hypothesis that metastatic progression of PCa requires glutaminolysis. This phenomenon makes enzymes of Gln metabolism highly promising, therapeutic targets. Unsurprisingly, several glutaminase small molecule inhibitors have been developed and some of them are currently being evaluated in clinical trials [59].

To control Gln metabolic hierarchy, carbohydrate restriction diets resulting in moderate ketosis have shown effect on stabilization of cancer remission [24]. Such deprivation can be enhanced *via* chemical extracorporeal blood treatment arranging low glucose and Gln in dialysate [60]. Such process should adversely damage tumor angiogenesis, and might be accompanied by application of conventional chemotherapeutics. We anticipate that this methodology merits further investigation and could be helpful particularly for therapy of poor-prognosis metastatic PCa exhibiting high glutaminolysis demands.

## 4. Ser (2-amino-3-hydroxypropanoic acid)

Recent studies have highlighted the importance of Ser biosynthetic and metabolic pathway for PCa making this non-essential amino acid a potential therapeutic target for its treatment [25,61]. Ser together with Gly are vital components in the anabolic building blocks for the generation of glutathione, nucleotides, phospholipids, and other metabolites. An increased synthesis of Ser was found to be a marker of poor prognosis of subjects suffering from PCa [15]. Up to this date, phosphoglycerate dehydrogenase (PHGDH), the first enzyme of the *de novo* Ser synthesis pathway, was found to be amplified in distinct types of cancer [62,63]. Therefore, PHGDH is considered another druggable target for development of small molecule inhibitors as evidenced by Pacold et al. [64].

### 4.1. SOG pathway

Fraction of the synthesized Ser is utilized for production of ATP in a pathway comprising *de novo* Ser synthesis, one carbon (folate) metabolism and Gly cleavage system (termed SOG pathway). Ser provides one-carbon units to THF to form 5,10-methylene-THF and, subsequently, 5-methyl-THF that is an intermediate in the methylation of homocysteine (Hcy) to methionine (Met), *via* Hcy methyltransferase (Met synthase). Schematic depiction of SOG pathway is shown in Fig. 3.

Clinical studies with stable isotopic tracers suggest that virtually all of the methyl groups used for the total body remethylation of Hcy are derived from Ser [65]. This ensures sufficient Met pool for Met cycle, subsequent synthesis of major methyl-donor SAM [66], and also for the formation of Gly, cysteine (Cys), taurine (Tau) and phospholipids [67]. Therefore, it is obvious that the regulation of Ser metabolism is of utmost importance for the tight control of epigenetic processes, particularly DNA methylation [66] that is crucial for controlling the majority of cellular functions.

At the gene expression level, SOG pathway enzymes are up-regulated in up to 9% of PCa cases. Noteworthy, it was shown that expression of *Myc* and its down-stream targets, as well as *TMPRSS2-ERG* fusion and Gleason score positively correlate with the pathway signature of PCa cells [15].

In SOG pathway, THF is consumed during conversion of Ser to Gly. As discussed above, using THF antimetabolite MTX, Ser-to-Gly conversion can be inhibited. This phenomenon resulted in the in the dose-dependent antiproliferative effects in metastatic PCa (PC-3) cells [15]. Moreover, MTX-administered cells exhibited no changes in glycolysis and OXPHOS pathways; however, massive inhibition of purine synthesis and ATP/adenosine diphosphate concentration occurred due to Ser-to-Gly deregulation.

### 4.2. Glycolysis and mitochondrial metabolic pathways

Pathways driving aerobic glycolysis and the biosynthesis of Ser and Gly are interconnected through the embryonic form of pyruvate kinase (PKM2) that catalyzes the final step in glycolysis generating pyruvate and ATP. Single switch to PKM2 is necessary for the shift from OXPHOS to glycolysis as was described for a variety of cancers, including PCa [26,68]. The enhanced glycolysis can decrease reactive oxygen species (ROS) and promote the pentose phosphate, and Ser/Gly synthesis pathway, which are both linked to tumorigenesis of PCa [45,62,63,69]. Ser can also act as an allosteric activator of PKM2. This phenomenon results in accumulation of glycolytic metabolites under conditions of Ser deprivation and consequent channeling them into the Ser biosynthesis [16,70]. Another enzyme crucial for the feeder reactions of carbon from TCA to crucial biosynthetic processes is phosphoenolpyruvate carboxykinase isoform 2 (PCK2) that catalyzes the conversion of oxaloacetate to phosphoenolpyruvate (PEP) [71]. PCK2 is critical for metabolic switch and the maintenance of tumor-initiating cells (TICs) playing vital role in progression and metastasis of PCa. Zhao et al. revealed that TIC-enriched PCa cells utilize more glucose and secreted more lactate than TIC-low clones [72]. Inhibition of PKM2 activity channeled more carbon through PEP to Ser synthesis for TICs, while the elevation of PCK2 activity enriched TICs through reducing the TCA cycle, ROS level, and production of citrate and acetyl-coenzyme A. Moreover, reported datasets indicate that PCa patients exhibiting higher PCK2 expression develop more aggressive PCa phenotype with lower survival rates (Fig. 4). These data indicate that PCK2 is a potential target for novel therapies targeting TICs.

### 4.3. Zinc metabolism and its linkage to metabolism of amino acids

Failure in intracellular zinc accumulation is a key hallmark in prostate carcinogenesis. In our study, PNT1A, 22Rv1, and PC-3 cell lines, depicting different stages of PCa progression, and their zinc-resistant counterparts were established and used to examine the impact of the intracellular increase in Zn(II) ions on distinct phenotypic parameters [19]. Interestingly, it was found that long-term zinc treatment re-routes cell metabolism from benign to more malignant phenotype. PCa cell lines universally displayed high accumulation of aspartate (Asp) and Sar and depletion of essential amino acids. Noteworthy, increased Asp/Threonine (Thr), Asp/Met, and Sar/Ser ratios were associated with malignant phenotype. This shed light onto the potential use of high-throughput analysis of intracellular amino acids patterns for diagnostic and prognostic purposes.

Despite above mentioned, serum Ser level as well as the levels of metabolites along the choline oxidation pathway were not found to be associated with PCa risk [73]. Nevertheless, it should be noted that individuals with a high Gly/Ser ratio were at a decreased risk of

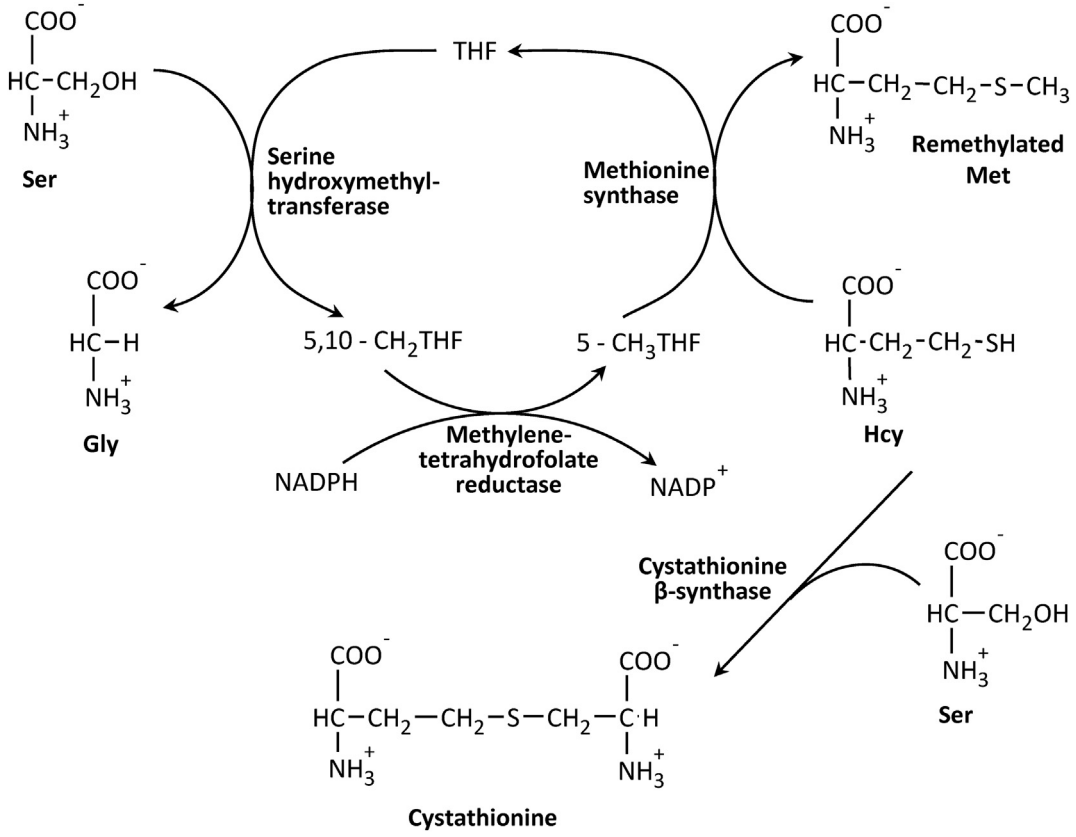


**Fig. 3.** Schematic illustration of SOG pathway. 5,10-$CH_2THF$ – 5,10-methylenetetrahydrofolate, 5-$CH_3THF$ – 5-methyltetrahydrofolate. Adapted and modified according to Davis et al. [65].

developing PCa. This phenomenon indicates that Gly/Ser metabolic pathway deserves a detailed investigation that could provide interesting insights into the biology of PCa development.

## 5. Proline (pro, pyrrolidine-2-carboxylic acid)

Pro is a non-essential imino acid with important roles in primary metabolism of carbon and nitrogen, protection against osmotic and oxidative stress, protein chaperoning, cellular signaling, apoptosis and adaptation to nutrients. Pro is also necessary for protein synthesis and structure, biosynthesis of amino acids and polyamines, wound healing, ROS scavenging, and immune response [74,75]. It has been described that nutrient formulations comprising Pro exhibit inhibitory activity in distinct PCa cells and xenograft models [76,77]. On the other hand, we have identified elevated urinary Pro levels in patients with diagnosed PCa, whereas virtually no Pro was identified in urinary specimens collected from subjects with no evidence of malignancy [78]. Since PCa cells generally tend to accumulate Pro to scavenge ROS (discussed below), such contradiction could be explained by the minor role of Pro within the nutrient mixture (or marked synergistic effect of mixture components).

### 5.1. Pro and apoptotic signaling

Pro catabolic pathway takes place in mitochondria, where Pro is oxidized to Glu through P5C (pyrroline-5-carboxylate) in a two-step enzymatic reaction catalyzed by proline dehydrogenase/proline oxidase (PRODH/POX) and P5C dehydrogenase (P5CDH). Conversely to this reaction, P5C synthetase (P5CS) and P5C reductase (PYCR) convert Glu into Pro. This pathway has been shown to be double-edged sword acting either as PCa suppressor by initiating ROS-mediated apoptosis, or as tumor survival factor through ATP production or ROS-induced

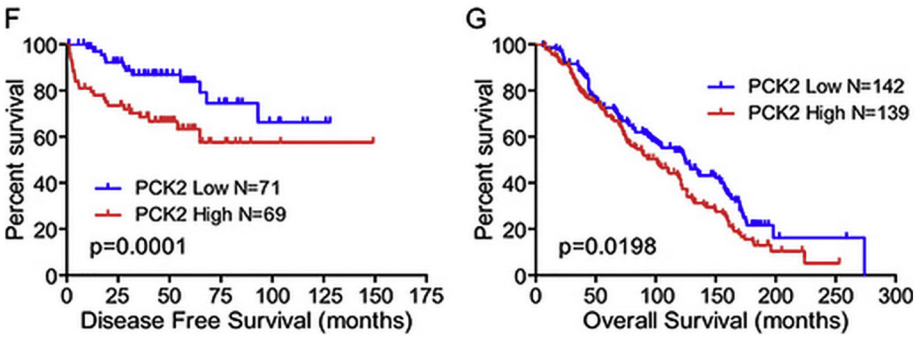


**Fig. 4.** PCa datasets indicating a role of PCK2 expression for a development of more aggressive PCa phenotype with lower survival rates. Adapted and modified from Zhao et al. [72].

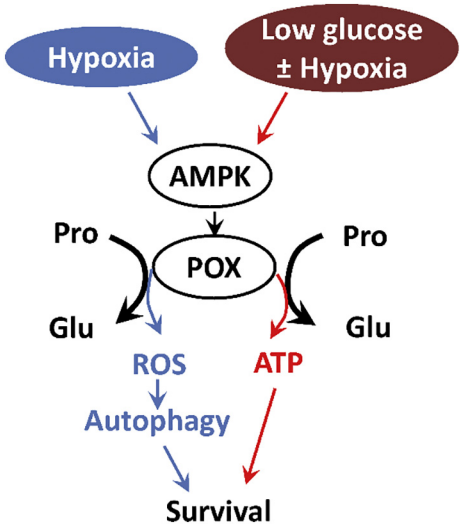


**Fig. 5.** Differential functions of POX under hypoxia and low glucose conditions. Hypoxia, low glucose, and combined low glucose and hypoxia upregulated POX through the same mechanism: the AMPK pathway. Under low glucose condition, POX is used preferentially for ATP production, while under hypoxia with adequate glucose POX mediated ROS production. Adapted and modified from Liu et al. [27].

autophagy (Fig. 5 [79–81]).

Pro biosynthesis was also identified as crucial for maintaining pyridine nucleotide levels by connecting the Pro cycle to glycolysis and pentose phosphate pathway [82], and therefore might provide a promising target for PCa therapy.

### 5.2. Pro and ROS scavenging

Pro acts as efficient ROS scavenger and was found to inhibit apoptosis induced by oxidative agents [83]. In metastatic PCa (PC-3) cells three-times higher content of Pro was found in comparison to normal prostatic cells, corresponding to the intrinsic chemoresistance of PC-3 cells to those agents [28]. Interestingly, pre-incubation with Pro increased the tolerance of normal cells to $H_2O_2$. Protective activity of Pro against ROS can be inhibited by knocking-down PRODH. This process leads to attenuated phosphorylated levels of Akt and FoxO3a and decreased cell survival. These data highlight the importance of Pro catabolism not only for producing the building blocks crucial for rapidly proliferating PCa cells, but also for their susceptibility to the environmental stressors (chemo-, radio-therapy). In recent years, several competitive PRODH inhibitors have been developed (*L*-tetrahydrofuroic acid, 5-oxo-2-tetrahydrofurancarboxylic acid or *N*-propargylglycine) [84,85]. Nevertheless, further investigation might be done to develop novel more effective and less toxic PCa therapeutics.

## 6. Arginine (Arg, 2-amino-5-guanidinopentanoic acid)

Arg is a semi-essential amino acid synthesized from Gln, Glu and Pro *via* the intestinal-renal axis. Arg degradation occurs *via* multiple pathways that are initiated by arginase, Arg:Gly amidinotransferase, and Arg decarboxylase. These pathways produce nitric oxide, polyamines, Pro, Glu, creatine, and agmatine with each having enormous biological importance. Arg is a nutritionally essential amino acid vital for spermatogenesis, embryonic survival, foetal and neonatal growth, as well as maintenance of vascular tone and hemodynamic [86]. Arg can be also metabolized by the nitric oxide synthase (NOS), to generate the free radical nitric oxide (NO) and citrulline. In the prostate tissue NO has a crucial physiological role for smooth muscle tone and proper secretory functions [87].

### 6.1. Inhibition of Arg metabolism as therapeutic target

It is known that stimulated metabolism of Arg within PCa tissue may contribute to the growth, angiogenesis, metastasis, and tumor-related immunosuppression [88,89]. Levels of the inducible form of NOS (iNOS) and arginase are therefore frequently up-regulated in prostate tumors compared to hyperplastic prostate [29,90]. Therefore, it is not surprising that strong iNOS expression was found to be a predictor for poor survival of PCa patients [91]. Treatment of PCa cultures with inhibitors of NOS or arginase resulted in activation of CD8 lymphocytes, prolonged their survival and restored their lytic capacity suggesting the role of Arg metabolism in tumor-associated immunosuppression [29].

### 6.2. Arg deprivation

Arg deprivation has been studied as a potential anticancer therapy, however with a limited success. Despite that, recent development of PEGylated arginine deiminase (ADI-PEG 20) enlarged possibilities of Arg deprivation in tumors [30]. PCa tissues have been shown to frequently lack expression of argininosuccinate synthetase (ASS), a ubiquitous enzyme involved in the two-step synthesis of Arg from citrulline [92]. Unable to synthesize their own Arg, ASS-deficient cells depend on relatively inefficient amino acid transporters [93]. Arg deaminase (ADI) isolated from *Mycoplasma* degrades Arg into citrulline. In native form, ADI is unstable and highly antigenic. PEGylation (in ADI-PEG 20 formulation) increases ADI stability and decreases its immunogenicity allowing to be used for decreasing of plasmatic Arg to undetectable levels. Due to the lack of ASS, ADI-PEG 20 induces a late caspase-independent cell death in CWR22Rv1, but not LNCaP *in vitro* [94].

Noteworthy, in 2018, ADI-PEG 20 completed Phase III clinical trial for hepatocellular carcinoma, exhibiting a significant prolongation of overall survival in patients with successful depletion of Arg [30]. Hopefully, further tests of Arg deprivation for PCa management will be conducted to extend the therapeutic possibilities.

## 7. Leucine (Leu, 2-amino-4-methylpentanoic acid)

Leu is an essential amino acid known to be important for protein synthesis [95]. Leu activates the mTOR signaling pathway that controls mRNA translation, ribosome biogenesis, autophagy, and cell metabolism. In PCa deregulation of mTOR contributes to tumor progression and stimulation of a castration resistance [31]. Leu is internalized by proteins belonging to a complex *L*-type amino acid transporters (LATs) family. Interestingly, LAT1 and LAT3 have been found up-regulated during distinct stages of PCa pathogenesis. In PCa xenografts, knock-down of LATs inhibits cell cycle progression and tumor growth and led to a spontaneous regression of metastasis [32]. Metastatic (LNCaP and PC-3) cells administered with Leu analogue 2-aminobicyclo-(2,2,1)-heptane-2-carboxylic acid (BCH) that allosterically blocks LATs exhibit a significant decrease in cell growth and viability and display arrests of cell cycle in $G_0$-$G_1$ phase. Moreover, microarray screening revealed that BCH down-regulates cell-cycle-check-point genes *UBE2C*, *CDC20* and *CDK1* and up-regulates *ID1,3,4* transcription factors inhibiting their transcription activation. It is worth to note, that the BCH-down-regulated genes found in PCa cell lines have also been found to be up-regulated in metastatic PCa specimens [32,95]. These findings indicate that targeting of LAT1/3 could be a promising way for developing modalities for precise therapy of metastatic, castration resistant PCa *via* suppression of mTOR activity and M-phase cell cycle genes. Indeed, a wide spectrum of LAT family inhibitors has been developed and successfully tested in pre-clinical models (structures of selected LAT inhibitors are depicted in Fig. 6) [42]. However, since the LATs shares the majority of substrates, these inhibitors target all members of LAT family, which is highly undesirable for clinical translation. Therefore, intensive efforts might be made to develop inhibitors precisely targeting LAT1 and LAT3.

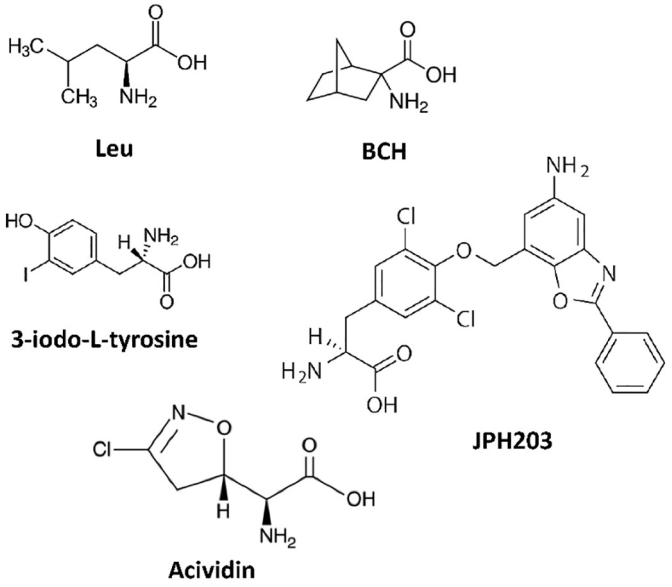


**Fig. 6.** Structures of Leu and selected LAT inhibitors.

## 8. Methionine (Met, 2-amino-4-(methylthio)butanoic acid)

Met is an essential amino acid that is necessary for growth, development, and homeostasis of mammalian cells. Met is synthesized endogenously either by homocysteine (Hcy) methylation in the presence of betaine co-factor and 5-methyl-THF or, putatively, through the polyamine biosynthesis pathway [96]. Catabolic product of Met is Sar, widely-discussed, non-invasive PCa biomarker and oncometabolite, whose importance for PCa is discussed below [38].

Together with Cys, Met is one of the two sulfur-containing proteinogenic amino acids, and its metabolites serve as major methyl donors. Accordingly, Met is involved in several biochemical pathways that provide molecular compounds for protein synthesis, chromatin and protein methylation, and synthesis of glutathione. In androgen-insensitive PCa cell lines, Met restriction stops proliferation and induces apoptosis [33].

Met metabolites provide superior sensitivity and specificity in multivariable prediction models for rapid biochemical recurrence following prostatectomy. Amounts of urinary products of Met catabolism correlate with PCa progression status [34]. Hence, the quantitation of Met metabolites as biomarkers would significantly increase the ability to predict aggressive PCa features and risk of early biochemical recurrence over existent clinical variables including serum PSA, biopsy and Gleason score.

Alterations in Met metabolism and Met dependency have been described in numerous cancer cell lines. Unlike normal cells, tumor cells are mostly not able to utilize Hcy as Met precursor. Met restriction blocks the cell cycle and induces apoptosis in metastatic (PC-3 and DU-145) PCa cells [33,35]. Poirson-Bichat and coworkers have demonstrated that proliferation rate of PC-3 cells is greatly reduced in Met-free medium, while proliferation rate of DU-145 cells is affected only slightly [97]. Addition of Hcy mildly increases the proliferation rate of PC-3 cells, while proliferation of DU-145 cells can be fully recovered. In PC-3 murine xenografts fed by Met-free Hcy-rich diet together with injection of Met analogue ethionine, slower growth of the tumor was observed suggesting usability of Met deprivation diet in castration resistant PCa.

## 9. Tryptophan (Trp, 2-amino-3-(1*H*-indol-3-yl)propanoic acid)

Trp is an essential amino acid used for protein synthesis and as the precursor molecule for biosynthesis of serotonin. Serotonin may act as mitogenic factor involved in cancer growth and angiogenesis, cell migration, and metastasis [98]. Serotonin-producing neuroendocrine cells are found in normal prostate tissue, as well as in PCa specimens. These cells are more commonly encountered in high-stage and high-grade PCa, with the highest concentrations occurring in castration-resistant PCa [36].

It is known that as a consequence of Trp shortage, T-lymphocytes undergo proliferation arrest [37]. Therefore, a degradation of Trp by indoleamine 2,3-dioxygenase (IDO) produced by multiple human tumors including PCa has been proposed as a mechanism favoring tumor escape from immune response [99]. Since PCa demonstrates high levels of IDO compared to benign hyperplasia, correlating with serum kynuerine/Trp ratio [100], this molecular mechanism might be utilized for enhancing options for PCa diagnostics.

## 10. Sarcosine (Sar, (2-methylamino)acetic acid)

Sar (also *N*-methylglycine) is an intermediate in Gly synthesis and degradation pathway. In 2009 Sar was delineated as a differential metabolite indicating presence of PCa. Furthermore, Sar level in prostate tissue, plasma and urine was found to be highly increased during PCa progression to metastasis. Intracellular Sar levels were also increased in invasive PCa-derived cell lines relative to benign prostate epithelial cells [38]. Due to its presence in urine it was proposed as putative non-invasive PCa marker, but later this conclusion has been disputed [101].

From other published studies, it follows that Sar and its metabolism are undoubtedly connected with PCa pathogenesis. Multiple amino acids mentioned in this review are involved in Sar metabolism, especially Gly, Cys, Met, Ser, Glu, Hcy and Tau. Scheme in Fig. 7 shows that Sar metabolism is interconnected with biosynthesis of nucleotides, control of redox environment, lipid metabolism, control of translation and DNA methylation [17].

### *10.1. Sar metabolism – small but mighty*

Sar metabolism comprises four parts – Sar pathway, folate cycle, Met cycle and transsulfuration pathway. Sar pathway has been found to be regulated by androgen receptor and *ERG* gene fusion product [38].

The major enzymes regulating metabolism of Sar are glycine *N*-methyltransferase (GNMT), sarcosine dehydrogenase (SARDH), and *L*-pipecolic acid oxidase (PIPOX). In cells, Sar is generated by the enzymatic transfer of a methyl group from SAM to Gly with the concomitant production of *S*-adenosylhomocysteine (SAH). This reaction is catalyzed by GNMT that is expressed at high levels in mammalian liver, exocrine pancreas and prostate [102]. The Sar-metabolizing enzymes, SARDH and PIPOX, catalyze the oxidative demethylation of Sar converting it back to Gly (Fig. 7) [103].

It was found that up-regulation of the polycomb group protein EZH2 that drives progression of PCa also stimulates production of Sar [104]. Interestingly, EZH2 knock-down in metastatic PCa cells (DU-145) leads to decrease in Sar and consequent inhibition of PCa invasiveness. Further, it was shown that Sar induces invasion of benign RWPE prostate cells [38]. Interestingly, knock-down of SARDH results in an increase in endogenous Sar together with a marked increase in invasiveness [38]. Khan et al. extended this study and shown that knock-down of SARDH also pronouncedly stimulates cellular proliferation and anchorage-independent growth [105], indicating plausible role of Sar in metastatic potential of PCa. Interestingly, when knocking-down another Sar *N*-demethylating enzyme PIPOX, the same cells increased invasiveness, but without effect on proliferation and anchorage-independent growth.

Attenuation of GNMT in DU-145 PCa cells results in a significant reduction in cell invasion, with a concomitant threefold decrease in the intracellular Sar compared to control (mock) cells. Interestingly, addition of exogenous Sar does not completely rescue invasive phenotype of these [105], most likely due to fast degradation rates of SARDH and

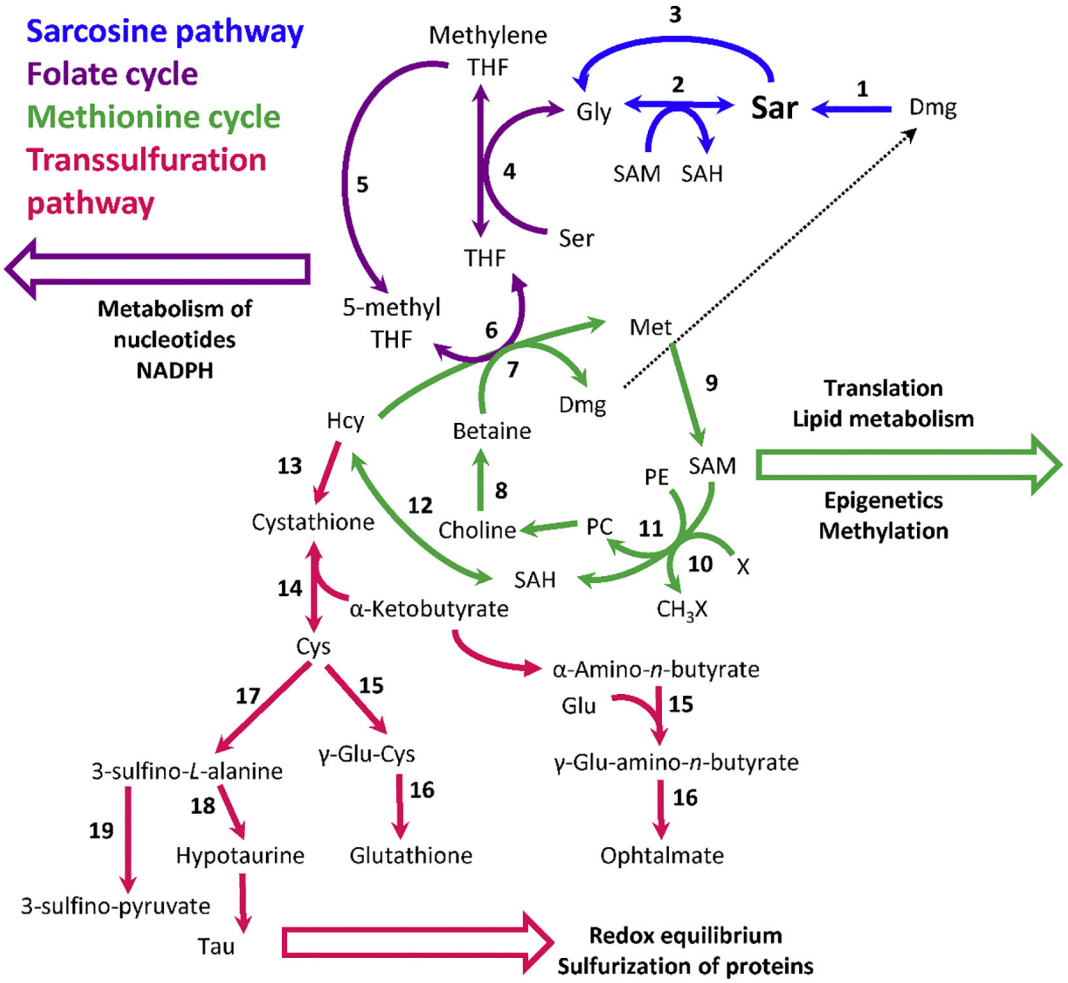


**Fig. 7.** Scheme of metabolical pathway of Sar biosynthesis and degradation to its non-methylated precursor Gly and its connection to other important metabolical pathways. Enzymes in scheme are numbered and depicted as follows: 1, DMGDH, dimethylglycine dehydrogenase; 2, GNMT, glycine-*N*-methyltransferase; 3, SARDH, sarcosine dehydrogenase; 4, SHMT1/2, serine hydroxymethyltransferase; 5, MTHFR, 5,10-methylenetetrahydrofolate reductase; 6, MTR, methionine synthase; 7, BHMT, betaine-homocysteine methyltransferase; 8, CHDH, choline oxidase; 9, MAT, methionine adenosyltransferase; 10, SAM-dependent methyltransferase; 11, PEMT, phosphatidylethanolamine methyltransferase; 12, AHCY, *S*-adenosylhomocysteine hydrolase; 13, CBS, cystathionine β-synthase; 14, CTH, cystathionase; 15, GCL, glutamate-cysteine ligase; 16, GSS, glutathione synthetase; 17, CDO1, cysteine dioxygenase 1; 18, CSAD, cysteine sulphinic acid decarboxylase; 19, GOT1, glutamate oxaloacetate transaminase 1. Dmg – dimethylglycine, SAM – *S*-adenosyl-methionine, SAH – *S*-adenosyl-homocysteine, PE – phosphatidylethanolamine, PC – phosphatidylcholine, and THF – tetrahydrofolate. Adapted and modified from Heger et al. [17].

PIPOX.

As shown in our pilot study, amino acids closely related to Sar metabolism, can significantly affect the expression of GNMT-encoding mRNA in prostate cells as well as their growth attributes [17]. These results indicate that Sar production is triggered by dimethylglycine (Dmg) administration more than by Gly. However, Gly, a well-known cancer-related metabolite, significantly influences the prostate cells amino acid patterns, shedding interesting light onto a use of distinct combinations of amino acids in deprivation therapy.

### *10.2. Influence of Sar supplementation on prostate cells*

Exogenous supplementation of cells with physiologically relevant amounts of Sar and its pathway-related amino acids triggers up- (particularly in the case of Dmg) or down-regulation (due to administration with Gly, Sar and Dmg) of GNMT [17]. This indicates that prostate cells can perform rapid reprogramming in a reaction to exogenous metabolites affecting Sar metabolic pathway.

To deepen this knowledge, we analyzed Sar effect on murine PCa xenografts [39]. It was found that Sar stimulates a tumor growth and reduces weight of treated mice. Interestingly, we found that Sar-exposed tumors accumulated Gly, Ser and Sar, and exhibited high expression of SARDH indicating the necessity for Sar metabolic degradation. High-throughput cDNA microarray revealed that Sar affects the expression of genes driving apoptosis, proliferation and cell cycle, indicating a direct effect on the growth of PCa.

In urine of PCa patients, Gly content negatively correlates with amount of Sar [78]. This suggests the need of PCa for utilizing Gly for Sar biosynthesis. Interestingly, in accordance with this fact, levels of Sar are decreased in elderly patients who have a higher probability to suffer from non-aggressive PCa with a lower ability to produce Sar due to dysregulation of the enzymes producing and catabolizing Sar [106]. These data indicate that intracellular Sar pool is a crucial oncometabolite affecting PCa development and progression to more aggressive phenotypes. Nevertheless, the molecular mechanism responsible for this phenomenon is not known. Further studies might be carried out to shed light onto the possible use of Sar for PCa diagnosis and stratification. Obvious importance of Sar metabolism for PCa aggressiveness may lead to investigation of specific inhibitors capable to inhibit biosynthesis of Sar. This might result in better efficiency in therapy of highly aggressive PCa.

## 11. Hydroxyproline (Hyp, 2*S*,4*R*)-4-hydroxypyrrolidine-2-carboxylic acid

Hyp is post-translational metabolite of Pro, vital for maintaining cell structure and function [107]. The unique ring structure of Pro and Hyp distinguishes them from other amino acids in terms of rigidity, chemical stability, and biochemical reactions [108]. Hyp is recognized as a substrate for the synthesis of Gly, pyruvate, and glucose, and also may scavenge oxidants and regulate the redox state of cells [40].

In past, total urinary Hyp has been shown to be more reliable than other markers indicating the presence and activity of PCa bone metastases [109] that are a major cause of PCa morbidity. Hyp is released into the circulation once PCa invades bone and is metabolized by the liver or excreted in the urine. Importantly, in PCa bone metastases, not only osteoid formations adjacent to tumor tissue, but also bone resorption is frequently accelerated. It is worth to note that the acceleration of bone resorption can be evidenced by the increase in urinary Hyp excretion, bone histomorphometry and the presence of lytic bones on radiographs. Based on these data, attempts have been made to use the urinary Hyp index (Hyp/mg creatinine) as biomarker of metastatic PCa [41]. Despite a number of supportive studies, Hyp (together with alkaline phosphatase) is considered to be only an auxiliary biomarker for the standard bone scintigraphy.

## 12. Taurine (Tau, 2-aminomethane-1-sulfonic acid)

Tau is a Cys derivative. Despite its lack carboxygroup it is sometimes mentioned among amino acids. In the organism, Tau is involved in conjugation of bile acids, antioxidation, osmoregulation, membrane stabilization and modulation of calcium signaling. It is essential for cardiovascular function, development, and function of skeletal system, retina and CNS.

In prostate and sex glands, Tau is synthesized by sulphone decarboxylase pathway [110]. In human prostate tissues, generally, an increased level of Tau can be found [111]. Madhu et al. demonstrated that Degarelix, a hormonal therapy used to decrease testosterone levels, concomitantly decreases Tau levels [112]. Moreover, Tang and coworkers found that in metastatic PCa (LNCaP and PC-3) cells Tau treatment decreases expression of prostate specific antigen and metastasis-related proteins (TIMP-1,2, MMP-9, VEGF) resulting in inhibition of cellular migration [42]. Tau also attenuates epithelial mesenchymal transition-related genes (*CDH1*, *CDH2*, *TWIST1*, *ZEB1*, *SNAI1*, and *VIM*) in LNCaP cells and inhibits human PCa cells metastasis [43]. Noteworthy, *N*-acyl Tau, a putative signaling molecule with a wide range of biological activities, was found to have antineoplastic and antiproliferative effect on metastatic PCa (PC-3) cells [44]. These data provide a solid foundation for future studies on Tau as a modality for auxiliary PCa therapy and suggest that Tau intake can be possible utilized to prevent PCa development.

## 13. Conclusions and future outlooks

So far multiple differences in PCa-specific metabolism of amino acids have been discovered. Moreover, with greater or lesser success some attempts to utilize this knowledge in PCa diagnostics, prognosis and/or therapy have been done. The most pronounced specificity of PCa cells is utilization of TCA cycle for anaplerosis. For ATP production the anaerobic metabolism is exploited, even when not in hypoxia. Consequently, PCa cells exhibit increased glycolysis and fatty acids synthesis. Due to the fact that in some PCa cases the biosynthetic pathways for specific amino acids are impaired, dietary or pharmacological deprivation of these amino acids has therefore a marked potential for inhibiting the PCa proliferation with no effect on non-malignant cells, similar to asparaginase in the treatment of leukemia and lymphoma. To enhance the dietary (mechanistic) deprivation of PCa cells, chemical extracorporeal removal of metabolites can be utilized and combined with standard chemotherapy. These approaches definitely merit further detailed investigation.

Finally, it should be noted that PCa is a highly heterogeneous disease with distinct metabolic alteration fingerprints. Therefore, only a detailed knowledge about these signatures can result in subsequent application of a proper therapeutic modality towards the new oncologic paradigm of precision medicine.

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## Conflict of interest

Authors declare none.

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