Organ specific cancer metabolism and its potential for therapy

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ABSTRACT

Targeting the metabolism of cancer cells has the potential to lead to major advances in tumor therapy. Numerous promising metabolic drug targets have been identified. Yet, it has emerged that there is no singular metabolism that defines the oncogenic state of the cell. Rather, the metabolism of cancer cells is a function of the requirements of a tumor. Hence, the tissue of origin, the (epi)genetic drivers, aberrant signaling, and the microenvironment all together define these metabolic requirements. In this chapter we discuss in light of (epi)genetic, signaling, and environmental factors the diversity in cancer metabolism based on triple-negative and estrogen receptor positive breast cancer, early and late stage prostate cancer, and liver cancer. These types of cancer all display distinct and partially opposing metabolic behaviors (*e.g. Warburg* versus *reverse Warburg* metabolism). Yet, for each of the cancers their distinct metabolism supports the oncogenic phenotype. Finally, we will assess the therapeutic potential of metabolism based on the concepts of metabolic *normalization* and metabolic *depletion*.

INTRODUCTION

Cellular metabolism describes a network of biochemical reactions that convert nutrients taken up from the environment into small molecules called metabolites. These metabolites serve as energy equivalents, redox co-factors, biomass building blocks, and substrates for DNA/RNA and protein modifications. In this way metabolism is involved in virtually any cellular process: *E.g.* proliferation and growth signaling, maintenance of ion gradients across membranes, or epigenetic remodeling via DNA/protein modifications. Hence, metabolism is highly tissue specific, because it is optimized to the function and cellular processes of the different organs. Moreover, metabolism is tightly interconnected with the upstream signaling network to directly link it with the regulation of dependent cellular processes.

Cancer cells induce a major reprogramming of essential cellular processes, which leads to novel abilities such as the evasion of growth control and cell death, the induction of motility and invasion, and the promotion of angiogenesis and to avoidance of immune destruction [1]. Since these processes are directly or indirectly linked to metabolism, the oncogenic transformation of cells requires metabolic changes. Specifically, metabolism fuels the altered cellular requirements of oncogenesis such as energy, redox-cofactors, biomass building blocks, or metabolites for DNA/protein modification. In this sense metabolic changes in cancer cells compared to non-malignant cells are a consequence of the cancer needs. Yet, there is also evidence that metabolic changes can be a cause of cellular transformation. It has been shown that the overexpression of certain enzymes such as 3-phosphoglycerate dehydrogenase leads to oncogenic transformation of non-malignant cells [2]. Also, epidemiological studies provide evidence that certain metabolic preconditions such as mutations in the enzyme fumarate hydratase, diabetes, or obesity are correlated with a significantly increased cancer risk [3-5].

Thus, targeting the altered metabolism of cancer cells in the context of the connected (epi)genetics, signaling, microenvironments, and tumor heterogeneity has the potential to identify novel therapeutic strategies [6-16]. Besides these factors, another essential parameter in the successful development of metabolism-based anti-cancer therapies is the organ in which the cancer arises. The organ of origin is important, because its tissue is optimized for a different cellular function with specific metabolic needs. Therefore, oncogenic transformation does not lead to one common set of metabolic changes but multiple metabolic changes that overlap only partially and inconsistently.

Here, we will review based on the examples of breast, liver, and prostate cancer the metabolic diversity of tumors. Subsequently, we will link the organ specific tumor metabolism to causal (epi)genetic and signaling changes.

BREAST CANCER METABOLISM

Breast cancer facts and current treatment

Breast cancer is the leading cause of cancer death in women worldwide [17]. Thereby, 90% of all breast cancer deaths are caused by distant metastases to lung, brain, or bone [18, 19]. Up to 30% of all patients diagnosed with early-stage breast cancer develop distant metastases and relapse [18].

Breast tumors are very heterogeneous at the morphological, molecular, and genetic level [20]. With respect to the treatment of breast cancer, three main therapeutic classes can be distinguished. Patients with estrogen receptor positive tumors (which include luminal A and B tumors) receive endocrine therapy [21, 22]. Endocrine therapeutics such as tamoxifen block the estrogen receptor and prevent estrogen induced growth signaling in the tumor. Patients whose tumors show human epidermal growth factor receptor *HER2* (also known as *ERBB2*) amplification receive anti-*HER2* therapy. Triple-negative breast cancers (lacking expression of estrogen receptor, progesterone receptor and *HER2*), which include primarily basal-like tumors, are currently treated with chemotherapy [21-23].

In this section we will discuss the metabolic features of triple-negative and estrogen receptor positive breast cancers (Figure 1). We focus on these two subtypes, because triple-negative breast cancers have been studied most intensively due to the lack of specific therapeutic approaches, their prevalence for distant metastasis [18], and their responsibility for overall high mortality rates [24]. Estrogen receptor positive (luminal) breast cancer, on the contrary, has led to a lower death incidence rate than triple-negative breast cancer and specific treatment strategies exist, but it is the most frequently occurring subtype (about 70% of all breast tumors are estrogen receptor positive) [25]. Generally, the metabolism of these two subtypes differs dramatically: triple-negative breast cancers mostly display a classical *Warburg* metabolism, while estrogen receptor positive breast cancers are enriched for a *reverse Warburg* metabolism. This further shows the need to link genetic, molecular, and environmental specificities of cancer cells to their metabolic needs, to enable the development of targeted metabolism based therapies.

Triple-negative breast cancer

Many triple-negative breast cancers display a classical *Warburg* metabolism with high glucose uptake and increased lactate secretion even in the presence of oxygen. *In vivo* measurements of glucose uptake rates using fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) demonstrated that the highly glycolytic phenotype of triple-negative breast cancers is not an artifact from cell culture conditions [26-28]. In line with the increased glucose uptake, several studies have shown an increased expression of glucose and lactate transporters, as well as lactate dehydrogenase, which interconverts pyruvate and lactate [29-32].

There is also evidence that the glycolytic rate of triple-negative breast cancers correlates with tumor aggressiveness. A retrospective analysis of the Ki-67 nuclear stain, which is a measure for the proliferation index of tumors, with the maximal glucose uptake rates measured by FDG-PET showed a strong correlation of both parameters in triple-negative breast cancers [26]. In line with this finding a correlation between the expression of monocarboxylate transporter 4 (needed for lactate secretion) and clinical outcome has been discovered [29]. Interestingly, while lactate dehydrogenase A is ubiquitously highly expressed in many breast tumors, it has been shown that lactate dehydrogenase B is essential for triple-negative breast cancers and co-expressed with monocarboxylate transporter 1 [32]. This is surprising, since lactate dehydrogenase B is believed to

preferentially convert lactate to pyruvate [33, 34]. Yet, another study showed that the knockdown of lactate dehydrogenase B similar to the knockdown of lactate dehydrogenase A increased oxygen consumption [35], which is unexpected since these enzymes preferentially use either pyruvate or lactate as a substrate. Thus, the metabolic role of lactate dehydrogenase B in triple-negative breast cancer remains to be elucidated.

The glycolytic phenotype of triple-negative breast cancer correlates with the proliferation index. This implies that glycolysis is important to fuel the energy, redox, or biosynthetic needs of fast growing tumors. Yet, it is currently not clear which of the three metabolic needs is most important for triple-negative breast cancers. Interestingly, activation of oxidative metabolism in triple-negative breast cancers led to decreased metastasis and decreased tumor growth [36]. This activation was triggered by increasing the activity of complex I of the respiratory chain, which results in an increased NAD^+/NADH ratio [36, 37]. Santidrian *et al.* correlated the increased NAD^+/NADH ratio with decreased mTORC1 activity [36] and subsequently increased autophagy [36]. These data argue for a small dynamic range of redox metabolism in triple-negative breast cancer, implying that any imbalance between reduced and oxidized redox cofactors might hamper tumor growth and that only the combination of decreased oxidative phosphorylation with increased glycolysis allows fast proliferation in certain types of triple-negative breast cancers.

Triple-negative breast cancers have been shown to display an increased uptake of glutamine and cholesterol, while the *de novo* synthesis of these metabolites was decreased [38-40]. Timmerman *et al.* demonstrated in a subset of breast cancer cells -which was highly enriched for the triple-negative subtype- that targeting the activity of the xCT glutamate-cystine antiporter (which mediates the exchange of extracellular L-cysteine and intracellular L-glutamate across the cellular plasma membrane) reduced tumor growth *in vivo* and *in vitro* [39]. Recent studies also found that estrogen receptor negative breast cancers (which include triple-negative breast cancers) have a low glutamine synthetase activity [40], resulting in a significantly increased glutamate-to-glutamine ratios compared to normal tissue [41]. Contrary to triple-negative breast cancer, estrogen receptor positive breast cancers have a high glutamine synthetase activity and increased glutamine secretion [40]. Furthermore, cholesterol storage in the form of cholesterol esters produced by acyl-CoA:cholesterol acyltransferase and cholesterol trafficking was increased in triple-negative breast cancer [38].

In contrast to the decreased *de novo* synthesis of glutamine and cholesterol, many triple-negative breast cancers activate the serine-glycine biosynthesis pathway. This is mainly caused by gene amplification or expression increase in the enzymes of the serine-glycine pathway such as 3-phosphoglycerate dehydrogenase [42-44]. Interestingly, in non-transformed breast cancer cell lines 3-phosphoglycerate dehydrogenase is rate limiting for serine biosynthesis [42]. This is opposite to the liver where it has been found that phosphoserine phosphatase is rate limiting [45]. This difference could be explained by low intra cellular serine levels in the breast compared to the liver and thus full activity of phosphoserine phosphatase (which is feedback-inhibited by serine) [42]. Corroborating the relevance of alterations in the serine pathway, increased expression of 3-phosphoglycerate dehydrogenase and phosphoserine aminotransferase 1 are correlated with a decreased relapse-free time and reduced overall survival of breast cancer patients [44]. Moreover, the overexpression of 3-phosphoglycerate dehydrogenase, phosphoserine aminotransferase 1, serine hydroxymethyltransferase, or glycine dehydrogenase provoked an oncogenic transformation of non-malignant cells *in vitro* [43, 46, 47].

Currently, it is not well understood how alterations in serine-glycine metabolism support tumor proliferation. On one hand, serine hydroxymethyltransferase, and glycine dehydrogenase both provide 5,10-methylene-THF, which is an important cofactor-precursor for nucleotide biosynthesis and DNA methylation; and both processes are increased in many tumors [2, 48]. Moreover, the first chemotherapeutic agents (which are chemical derivatives are still used today) were anti-folates and inhibit enzymes in the folate pathway, such as dihydrofolate reductase [49]. Dihydrofolate reductase provides THF, which is a precursor to 5,10-methylene-THF. On the other hand, the proliferation defect induced by the knockdown of amplified 3-phosphoglycerate dehydrogenase in triple-negative breast cancers could not be rescued with the supplementation of extracellular serine [42, 43], despite the fact that extracellular serine can fuel folate metabolism [50]. Thus, increased supply of serine does not seem to be the critical function of 3-phosphoglycerate dehydrogenase amplification. Interestingly, Possemato *et al.* suggested that the coupling of serine biosynthesis to α -ketoglutarate production could be important in 3-phosphoglycerate dehydrogenase amplified cells [42]. Thus, multiple roles of serine-glycine metabolism for breast cancer proliferation are possible, and the identification of precise mechanisms requires further study.

In contrast to the success of an anti-folate therapy, several epidemiological studies showed that the risk of breast cancers (and maybe particularly estrogen receptor-negative breast cancer [51]) is reduced with increased dietary levels of folate [51-56]. This controversial finding of intracellular serine-glycine-folate metabolism versus extracellular, nutrient-derived folate clearly demonstrates the need to not only identify metabolic differences in diseased versus healthy cells, but also to understand the regulation of metabolism based on nutrient availability. This important link between nutrient availability and intracellular metabolism is further highlighted through epidemiological studies that associate obesity with the prevalence of triple-negative breast cancer [57].

Estrogen receptor positive breast cancer

In contrast to triple-negative breast cancers, many estrogen receptor positive breast cancers display the so-called *reverse Warburg* effect. The *reverse Warburg* effect in estrogen receptor positive breast cancers includes the metabolic interaction between tumor cells and stromal cells. Thereby, cancer cells promote the metabolic reprogramming of stromal cells such as fibroblasts into cancer-associated fibroblasts [58]. Specifically, fibroblasts co-cultured with breast cancer cells displayed decreased caveolin 1 expression, and induction of HIF1 α and NF κ B [59]. Notably, HIF1 α stabilization can lead to aerobic glycolysis and subsequent increase in lactate and pyruvate secretion via the overexpression of the monocarboxylate transporter 4 [60]. In turn, the cancer cells use the secreted lactate and pyruvate to fuel their tricarboxylic acid cycle [60]. Thus, in this complex interaction, the cancer-associated fibroblasts display a glycolytic metabolism, while the cancer cells rely on oxidative metabolism. The *in vivo* occurrence of *Warburg* versus *reverse Warburg* effect was shown based on immunostaining of several indicative proteins such as glucose transporter 1, monocarboxylate transporter 4, and ATP synthase in tumoral and stromal tissue microsections [30]. Interestingly, this symbiotic behavior of lactate catabolizing and anabolizing cells does not only exist between tumor cells and cancer-associated fibroblasts, but also between tumor cells residing in hypoxic regions and tumor cells residing in oxygenated regions [61].

In conclusion, triple-negative and estrogen receptor positive breast cancers show very diverse metabolic phenotypes with rapidly proliferating triple-negative breast cancers displaying a pronounced glycolytic phenotype. This raises the question whether fast proliferation requires a glycolytic metabolism? In line with this notion is the fact that luminal B estrogen receptor positive breast cancers, which are defined by a high proliferative index, display less often a *reverse Warburg* metabolism compared to slow proliferating luminal A estrogen receptor positive breast cancers [30]. Thus, a glycolytic metabolism might promote fast proliferation, yet we still need to understand which metabolic requirement it fulfills.

Genetic alterations in breast cancer and their connection to metabolism

In addition to the proliferative index of tumors, genetic alterations define metabolic needs of breast cancer cells. The most commonly mutated gene in breast cancer is p53 [62]. P53 is a major regulator of apoptosis, senescence, and cell cycle arrest. However, p53 also regulates various enzymes in metabolism and can promote an oxidative metabolism over a glycolytic metabolism [63]. Yet, there is also evidence that certain metabolic targets of p53 such as hexokinase rather promote than inhibit glycolysis [63]. Thus, alterations in p53 status might be able to contribute to both, the *Warburg* metabolism of triple-negative breast cancer and the *reverse Warburg* metabolism of estrogen receptor positive breast cancer.

The oncogene MYC is a major regulator of glutamine and glucose metabolism [64]. Specifically, MYC promotes catabolism of glutamine (for instance, through glutaminase 1 regulation) [65]. Since many triple-negative breast cancers have elevated MYC expression [66], this could explain their shift from glutamine synthesis to glutamine uptake. Additionally, MYC induces glycolysis by up-regulating lactate dehydrogenase [65] and glucose uptake [67]. Yet, glucose metabolism is not only under the control of MYC and p53. Alvarez *et al.* demonstrated the importance of the genetic drivers by determining glucose uptake in breast cancer tumors by FDG-PET. Specifically, Akt- and MYC- driven tumors exhibited higher FDG uptake than Wnt1-, HER2-, or RAS- driven tumors, although without a difference in tumor growth. At molecular level, FDG uptake and the activity of the above-mentioned pathways was generally associated with hexokinase-2 and HIF-1 α stabilization, whereas an association with glucose transporter 1 was only observed in Akt- and HER2-driven tumors [67].

Additionally, the amplification/overexpression of the genetic driver *HER2* defines fatty acid metabolism in one subtype of breast cancers: It has recently been suggested that *HER2* directly phosphorylates and thereby activates fatty acid synthase [68]. Thus, fatty acid synthase inhibitors might be potent drugs in *HER2* amplified breast tumors [68].

LIVER CANCER METABOLISM

Liver cancer facts and current treatment

Under normal physiological conditions the liver performs essential functions such as processing nutrients, degradation and storage of body fuels and clearance of toxins. To fulfill these functions, hepatocytes are highly specialized and organized in periportal or perivenous hepatocytes, this is known as functional zonation. Mostly affected by this zonation are processes like ammonia detoxification, glucose/energy metabolism and xenobiotic metabolism.

Hepatocellular carcinoma (HCC) is one of the deadliest and most common cancers worldwide [69]. In the development of HCC, nutrition and metabolic related factors like alcohol consumption, aflatoxin contamination in food [70], the gut microbiota [71], diabetes [72] and bodyweight [73] influence initiation and progression of HCC. To treat HCC is difficult, because its onset often occurs on top of an underlying liver disease such as hepatitis B or C virus infection, alcoholic liver disease, or non-alcoholic fatty liver disease. Depending on the stage of the cancer and the liver function, surgical resection, liver transplantation and radiofrequency ablation are options for patients with early stage disease. For advanced liver cancer the multi-kinase inhibitor Sorafenib is to-date the only approved agent [69, 74]. In the following sections, we focus on the metabolic features of healthy versus cancerous liver tissue and the connected (epi)genetic and signaling drivers (Figure 2).

Metabolic alterations in liver cancer

The most fundamental change in HCC metabolism is the switch from glucose production (gluconeogenesis) to glucose usage. For more than 50 years it has been described that in liver cancer compared to normal liver cells the activity of glucose-6-phosphatase, phosphoenolpyruvate-carboxykinase, as well as fructose-diphosphatase and hence gluconeogenesis is decreased or absent [75-79]. Ma *et al.* showed in 2013 that this lack of gluconeogenesis might occur due to the decreased expression of 11 β -hydroxysteroid dehydrogenase type 1 and an increased expression of 11 β -hydroxysteroid dehydrogenase type 2. These enzymes control the activity of glucocorticoids [80]. Glucocorticoids promote gluconeogenesis, but in liver cancer cells the altered expression of 11 β -hydroxysteroid dehydrogenase1/2 results in the insensitiveness of liver cancer cells to endogenous glucocorticoids [81]. Moreover, it was shown that Stat3-mediated activation of the microRNA23a suppresses gluconeogenesis by targeting glucose-6-phosphatase expression [79]. Consistently, restoring gluconeogenesis by dexamethasone treatment showed significant inhibition of *in vivo* tumor growth [80]. A block in gluconeogenesis might contribute to the survival of HCC cells by increased usage of glycolysis and pentose phosphate pathway due to accumulation of glucose-6-phosphate [79]. In addition to the fundamental loss of gluconeogenesis, it was demonstrated that glycogenesis also decreases during the oncogenic transformation of liver [75, 78, 82]. Both phenomena indicate that the catabolism of glucose, compared to its anabolism and storage in the form of glycogen, is essential for liver cancers.

Further evidence for the importance of glucose catabolism in liver cancer has been described since the sixties. Rapid proliferation was correlated with increased activity of fetal-type liver enzymes like hexokinase 2, glucose-6-phosphate dehydrogenase and pyruvate kinase-M2 [78]. In accordance a decreased activity for adult-type liver enzymes like hexokinase 4, or pyruvate kinase-L was measured [83]. To enable a high glycolytic capacity, the liver cancer tissue must attain an enhanced uptake of glucose. While glucose transporter 2 is most important in healthy liver, the fetal glucose transporter 1 is upregulated in HCC, and its expression is correlated with HCC proliferation and invasiveness [84-87]. Moreover, patients with a high glucose transporter 1 expression showed higher α -fetoprotein (HCC tumor marker) and poorer differentiation compared to the glucose transporter 1 low-expression cohort [88]. Finally, FDG-PET imaging confirmed that the described alteration in the expression of glycolytic enzymes and glucose transporter results in an increased glucose uptake rate [88-90].

Besides glucose metabolism, glutamine metabolism is also significantly altered in liver cancer. The liver-type glutaminase 2, which catalyzes the conversion of glutamine to glutamate is almost absent or significantly decreased in human HCC [91]. Consistently, the expression of glutamine synthetase, which catalyzes the opposite reaction, is increased in HCC patients with β -catenin mutations [92-94]. Glutamine synthetase is a target gene of β -catenin and overexpression of glutamine synthetase is highly correlated with β -catenin mutations [92], which in turn is related to early-stage HCC [95]. Moreover, glutamine synthetase expression is correlated with HCC progression [93, 96]. Supporting the importance of glutamine metabolism in liver cancer, increased concentrations of glutamate and glutamine have been detected in human HCC in comparison to adjacent normal tissue [97]. Interestingly, glutamine synthetase expression is related to liver regeneration and therefore is observed during cirrhosis (a pre-state of liver cancer) [93, 98]. Thus, whether glutamine synthetase expression is a drug target or only a biomarker remains to be determined.

Differential lipid metabolism is an important risk factor in liver cancer [99-101]. Accordingly, the expression of stearoyl-CoA desaturase, a membrane protein of the endoplasmic reticulum that catalyzes the formation of monounsaturated fatty acids from saturated fatty acids, was found to be associated with aggressiveness of HCC [100-102]. Moreover, suppression of stearoyl-CoA desaturase could reduce proliferation in HCC cell lines in an Akt-dependent fashion [100]. One proposed mechanism for the correlation between stearoyl-CoA desaturase expression and HCC aggressiveness might be the systemic link to insulin signaling. Specifically, monounsaturated fatty acids could have an insulin-sensitizing function and thus affect glucose uptake, leading to enhanced capacity for cell proliferation [103]. In addition to desaturation of lipids, also *de novo* lipid synthesis was increased in liver cancer. Calvisi *et al* showed a progressive induction of mRNA and protein expression of fatty acid synthase, adenosine triphosphate citrate lyase, acetyl-CoA carboxylase, malic enzyme, stearoyl-CoA desaturase 1, 3-hydroxy 3-methylglutaryl-CoA-reductase, mevalonate kinase, and squalene synthetase, sterol regulatory element-binding protein 1 and 2, liver X receptors α and β , and carbohydrate responsive element binding protein. The induction of these enzymes was most pronounced in a patient cohort with poor survival outcome [100].

In conclusion, the loss of gluconeogenesis and potentially glycogenesis is a major factor in the metabolic reprogramming of transformed liver cells. Consequently, glycolysis and fatty acid synthesis are activated. This major switch implies that re-activation of gluconeogenesis has the potential to counteract liver cancer progression (see therapy section). Moreover, it is striking that many of the embryonic isoforms of enzymes such as hexokinase 2 are activated, while the adult isoforms are downregulated. This implies that the liver cancer cells use the embedded natural processes of embryonic proliferation to sustain their uncontrolled proliferation phenotype.

Genetic, epigenetic, and signaling drivers of Liver Cancer and their connection to metabolism

The most frequently mutated genes in liver cancer are p53 and β -catenin [104]. Also signaling pathways like EGFR, VEGFR, Met and intracellular mediators such as Ras and Akt/mTORC1 may play a role in HCC development and progression [104, 105]. With no common mutations in coding genes that can account for all cases of HCC, it is likely that epigenetic changes are key driving mechanisms of HCC development [106]. In line with this, aberrant DNA methylation patterns have been reported [107] and also histone deacetylase 2 is commonly upregulated in human HCC [108]. In this section we discuss how these genetic drivers are linked to metabolic changes in liver cancer.

The p53 status in liver cancer can contribute to the alterations in glucose and glutamine metabolism. Huang *et al.* identified CD147 as an important regulator of the *Warburg* metabolism in HCC cells via a p53 route [109]. Additionally, Hu *et al.* demonstrated that the down-regulation of glutaminase 2 is p53-dependent. Thus, the p53 status of liver cancer may contribute to the altered glucose and glutamine metabolism during oncogenesis [91]. Another enzyme involved in glutamine metabolism is the β -catenin target gene glutamine synthetase. Overexpression of glutamine synthetase is highly correlated with β -catenin mutation [92].

Mutant *EGFR* has been shown in other cancer types to activate Stat3 pathway by means of IL-6 upregulation [110]. This contributes to inhibition of gluconeogenesis through Stat3-mediated, glucose-6-phosphatase suppression in HCC [79].

Histone deacetylase 2 is commonly upregulated in HCC. Upon histone deacetylase 2 knockdown, glycolysis and lipid accumulation are decreased due to the inhibition of PPAR γ , ChREBP α , FAS and SREBP regulation [108]. Additionally, the knockdown of histone deacetylase 2 increased acetylation of p53 and in turn led to the expression of p53 target genes, which can counteract the metabolic requirements of liver cancer cells.

PROSTATE CANCER

Prostate cancer facts and current treatment

Prostate cancer is the most commonly diagnosed cancer in men in developed countries [17]. Whereas patients with well differentiated tumors can mostly be cured (9.1 % mortality after 10 years [111]), the outcome for patients with progressed and poorly differentiated tumors is detrimental (25.6% mortality after 10 years [111]).

Currently, there are several options to treat prostate cancer depending on its progression. At first, these therapies include androgen deprivation therapy, radical prostatectomy and different radiation therapies [112-114]. Advanced, relapsing and castration-insensitive prostate cancers are largely treated with therapies that target the androgen signaling pathway and immune therapy (reviewed in [115, 116]). In addition, more attempts to develop drugs that act on other prostate cancer targets, such as ETS-fusions, or the PI3K signaling pathway, or fatty acid metabolism, are reported [117, 118].

Prostate cancer originates in the peripheral zone of the prostate where about 70% of the cancer emerges in a multifocal manner [119]. Upon an inflammatory event, reactive oxygen species accumulation and certain driver mutations, normal epithelial cells progress through different stages to build an adenocarcinoma. These stages start with the build-up of prostatic intra-epithelial neoplasia, which then develops into an adenocarcinoma. The latter might become castration-insensitive and metastasizes, preferentially in bone (reviewed in [119]).

Initiation and progression of prostate cancer are highly coupled with metabolic rearrangements. In the following we divide these metabolic events into early changes (primary tumor-metabolism) and late stages (undifferentiated and castration-resistant prostate cancer metabolism) (Figure 3).

Early stage prostate cancer metabolism

In contrast to other tissues, normal prostate epithelial cells rely on aerobic glycolysis, because the tricarboxylic acid cycle enzyme m-aconitase (and thus glucose oxidation) is blocked by high intracellular zinc levels (*i.e.* zinc levels three to 10-fold higher than in other soft tissues [120-122]). As a consequence, citrate accumulates and is excreted into the prostatic fluid. In an early step during the transition from healthy to malignant tissue, prostate cells lose their ability to accumulate zinc due to the down-regulation of zinc transporters (mainly ZIP1) [122, 123]. Therefore, the block of the tricarboxylic acid cycle is relieved and the cells switch their metabolism to generate energy via oxidation of citrate and coupled respiration. Concomitant low glucose uptake rates (*i.e.* FDG-PET cannot be used to detect primary tumors; reviewed in [124, 125]) suggest that other substrates are fueling cancer growth. Specifically, a lactate-shuttle between cancer-associated fibroblasts and tumor-tissue was proposed [126], since cancer-associated fibroblasts express the monocarboxylate transporter 4 and tumors overexpress the monocarboxylate transporter 1 (*reverse Warburg effect*) [127-130]. This relationship allows the tumor to take up lactate and to convert it to pyruvate, which is processed in the tricarboxylic acid cycle. However, opposing this model, prostate tumors overexpress lactate dehydrogenase A [129, 131-133], which preferentially works in the direction of lactate production [33, 34]. Consistently, lactate dehydrogenase B, which catalyzes the lactate to pyruvate conversion, is suppressed [131, 134]. This is further functionally supported by experiments with hyperpolarized pyruvate, where *in situ* tumors convert pyruvate into lactate [135-137]. Thus, it is questionable whether cells *in vivo* exchange lactate or rather other substrates (*e.g.* pyruvate, since the K_m of monocarboxylate transporter 1 for pyruvate is lower than for lactate [126]). Specifically, a more systematic analysis of the cancer environment and consumption and secretion rates might be helpful in resolving this inter-cell-dependency.

However, the cell-cell interaction seems to support in any case oxidative phosphorylation, which is in line with a *reverse Warburg* metabolism. In addition, prostate cancer cells seem to induce peroxisomal branched-chain fatty acid oxidation (alpha-methylacyl-CoA racemase, D-bifunctional protein, acyl-CoA oxidase 3), which includes α -oxidation and a partial β -oxidation [129, 138-142]. Moreover, the short chain fatty acids, which then are released from the peroxisome might further fuel the TCA cycle by their full β -oxidation in the mitochondria. Although enzymes of mitochondrial β -oxidation are not increased in prostate

cancer [140], it has been shown that etomoxir-mediated inhibition of mitochondrial β -oxidation at the level of carnitine palmitoyltransferase 1 induces cell death in prostate cancer cell lines [143]. Interestingly, prostate cancer also induces fatty acid biosynthesis by overexpressing fatty acid synthase early during tumor progression without lipid accumulation [144, 145], which is further consistent with ^{11}C -acetate PET/CT experiments [146]. Why a futile cycle of simultaneous fatty acid oxidation and fatty acid synthesis is beneficial to prostate cancer cells remains an open question.

Later stage prostate cancer metabolism

Further dedifferentiation of the tumor is connected with a more pronounced expression of monocarboxylase transporter 1, lactate dehydrogenase A, altered cholesterol metabolism [147], as well as with a boost in fatty acid biosynthesis and associated enzymes (reviewed in [118]). Moreover, inhibition of fatty acid biosynthesis and oxidation was reported to inhibit tumor growth [143, 148, 149]. Yet, cancer cell lines, such as DU-145, LNCaP and PC-3 exhibit an elevated fatty acid uptake from the environment, which renders them less sensitive to inhibition of fatty acid biosynthesis [150-152]. This further underlines the importance of considering the microenvironment, which potentially modulates intracellular metabolism [152]. Additionally, high grade (Gleason > 7) and castration-resistant tumors seem to reactivate glycolysis, since FDG-PET and FDG-PET/CT studies indicate an increased glucose uptake compared to benign and low stage prostate cancers [153-157]. Accordingly, prostate cancer is affected by 2-deoxyglucose [158-160]. This is further in agreement with cell line studies, which show that the metastatic androgen-sensitive cell line LNCaP and the castration-resistant low-differentiation cell lines DU-145 and PC-3 are sensitive to glucose starvation [152] and that androgen signaling enhances the expression of glycolytic enzymes [161-163]. However, whether or not an increased expression of the glucose transporter 1 or other hexose transporters are causal for this phenotype is still a matter of debate, since histological data are inconclusive [164-167].

Interestingly, it was shown *in vitro* and in xenograft models that prostate cancer cell lines are highly dependent on the phosphofructokinase-fructose-bisphosphatase 2 isoform PFKFB4 and on glucose-6-phosphate dehydrogenase [152, 168]. Specifically, PFKFB4 drives the balance of glucose-6-phosphate and fructose-1,6-bisphosphate towards glucose-6-phosphate. Latter is used as a substrate in the glucose-6-phosphate dehydrogenase reaction, the initial step of the oxidative pentose phosphate pathway. This suggests that a substantial portion of the glucose taken up is channeled through the pentose phosphate pathway for reduction of NADP^+ and consequently glutathione disulfide, as well as for *de novo* nucleotide biosynthesis [168, 169]. Besides, prostate cancer still relies on oxidative phosphorylation, which is enforced by the interaction with cancer-associated fibroblasts as shown for PC-3 cells [127]. Consistently metformin, an inhibitor of mitochondrial complex I, provokes a decrease of proliferation with a subsequent activation of reductive glutamine metabolism *in vitro* and in a TRAMP mouse model [159, 170]. Moreover, a combinatorial therapy of metformin and an inhibitor of glutamine metabolism might be promising for therapeutics, since PC-3 and DU-145 cell lines are reportedly glutamine addicted [171, 172], and respiration and fatty acid biosynthesis could thus be inhibited simultaneously [170].

In sum, so far published data indicate that the first step of an oncogenic transformation of the prostate is a switch to oxidative metabolism. During prostate cancer progression to castrate-resistance this oxidative or *reversed Warburg* metabolism changes to a *mixed Warburg* metabolism, where both, glycolysis and respiration serve as sites for energy and biomass precursor generation.

Genetic drivers, signaling and microenvironment in prostate cancer and their connection to metabolism

In the past decades several drivers for prostate cancer and progression were identified at the genomic, transcriptional and protein-level [119, 173-182]. The acquisition of these driver mutations and subsequent tumor progression could either follow a linear pathway or a molecular diversity model as suggested by Rubin *et al.*, 2011 [178]. Early drivers are commonly thought to be loss of the transcription factor NKX3.1 protein expression, activation of the MYC transcription factor and TMPRSS2-ERG gene-fusions. These events are often followed by alterations in the PI3K signaling, RB signaling and RAS/Raf signaling, which render the tumor more aggressive [176]. Finally, androgen-resistance occurs, which is consistent with the fact that most metastatic tumors have an alteration in the androgen signaling pathway [173, 176, 180]. While there was much effort in mechanistically unraveling these signaling pathways and their interplay, there is less knowledge about their specific impact on prostate cancer metabolism.

As mentioned above, a key event in prostate cancer initiation is the down-regulation of zinc-transporters, which then allows the cancer to fully oxidize citrate. The regulation of zinc transporters in prostate cancer was shown to depend on the expression of the microRNA cluster miR-183-96-182, which correlates with Gleason score [183, 184]. Another mechanism involves the RAS responsive element binding protein-1 [185]. Specifically, it was found that RAS responsive element binding protein-1 is overexpressed early in prostate carcinogenesis and that it down regulates zinc-transporter 1. Although zinc-transporter 1 might be a target for therapy, currently no drug exists to activate this transporter [123]. Additionally, a low zinc level might be maintained in later stages by HoxB13-mediated induction of the zinc output transporter ZnT4[186].

The progressive switch of *reverse Warburg* metabolism to a *mixed Warburg* metabolism is mediated by a multitude of signaling pathways, which reportedly include p53 loss, PI3K/AKT activation, MYC overexpression, and androgen signaling. The links to metabolism for p53 loss, PI3K/AKT signaling and MYC were investigated with the focus on specific metabolic pathways; *i.e.* MYC induces glutaminase and proline synthesis via miR-23a/b [187, 188], the PI3K/AKT pathway up-regulates FASN expression [189, 190], and p53 loss induces mitochondrial aconitase expression [191]. The role of the androgen receptor in the induction of a *mixed Warburg* phenotype was more globally assessed. Increased androgen receptor signaling might directly or with the aid of other signaling pathways increase overall metabolic activity [161, 162, 167]. Specifically, AMPK and consequently PGC-1 α could be activated by androgen receptor-dependent CAMKK induction, which is connected to increased glycolysis and lactate excretion, but also mitochondrial biogenesis [161, 163]. Increased glycolytic metabolism is further supported by higher hexokinase 2 expression, which is at least partly triggered by androgen-receptor-dependent activation of PKA/CREB [162]. Interestingly, AMPK activation seems not to antagonize mTOR signaling status [161] and thus allows a mTOR-dependent induction of glucose-6-phosphate dehydrogenase and the oxidative pentose phosphate pathway [168], which allow an increased NADP⁺-reduction and nucleotide biosynthesis.

Besides, hypoxic environments and pseudo-hypoxia might play a pivotal role in the modulation of prostate cancer metabolism via HIF1 α stabilization. It was shown that HIF1 α generally upregulates lactate dehydrogenase A, mitochondrial aconitase, and more specifically fatty acid synthase in high grade tumors [192]. Corroborating this result β -arrestin 1 is up-regulated in high grade prostate cancer and stabilizes HIF1 α , which is connected to a reduction of succinate dehydrogenase A, fumarate hydratase, dihydrolipoamide dehydrogenase, dihydrolipoyl transacetylase and pyruvate dehydrogenase [193]. This was further accompanied with an up-regulation of glucose uptake and lactate secretion [193]. Overall this indicates that prostate cancer might partly promote anaerobic glycolysis and reductive carboxylation from glutamine in a HIF1 α -dependent manner.

In summary, the comparison between breast, liver and prostate cancer clearly shows that the tissue of origin has a substantial contribution to the definition of a transformed versus healthy metabolism. For example, the reactivation of respiratory metabolism in the prostate is of oncogenic potential while as well the highly glycolytic phenotype of triple-negative breast cancers sustains tumor proliferation. Beyond the tissue of origin it seems equally important to consider the (epi)genetic drivers, aberrant signalling and the microenvironment, since different subtypes of tumors from the same tissue result in a differential metabolism as described for breast cancer. Moreover, the metabolism within one tumor is not static, but -as highlighted for the prostate- it is a dynamic parameter that adapts to the requirements during tumor progression.

THERAPEUTIC OPPORTUNITIES OF CANCER METABOLISM

The central role of metabolism for all cellular processes in the cell defines it as a promising target for cancer therapy (Table 1), specifically because catalytic functions of metabolic enzymes are generally considered to be easily druggable by small molecules [15]. Metabolism is the downstream converging point of the highly interconnected signaling pathways, thus side-effects are less likely and resistance mechanisms harder to employ [7]. Moreover, metabolic changes are necessary to enable a certain carcinogenic phenotype. There are two concepts for metabolic drugs, which are given by *normalization* and *depletion*. In the concept of *normalization*, metabolic drugs enforce the redirection of the metabolic fluxes (which are the conversion rates of metabolites throughout the metabolic pathways) towards a normal metabolism as defined by healthy cells in the same tissue. In the concept of *depletion*, metabolic drugs inhibit a pathway that is predominantly essential for the tumor cells and thus they drain the metabolic requirements of the tumor.

The concept of *depletion* has a long-standing history in cancer treatment with anti-folates, nucleoside analogues, and asparaginase [49, 194, 195] as examples. The underlying principle for the use of anti-folates and nucleoside analogues is the dependency of fast proliferating cells on *de novo* DNA synthesis. Since not only cancer cells can display a fast proliferation, these drugs lead to a general collateral damage. Nevertheless, their efficiency and side-effects are similar to other non-metabolic chemotherapeutic agents such as paclitaxel, which inhibits mitosis [196, 197]. The expression of asparaginase is a more specific therapy than nucleoside analogues, since acute lymphoblastic leukemia are asparagine auxotrophs and depend on the uptake of sufficient amounts of asparagine. Thus the expression of asparaginase *depletes* the availability of asparagine because it degrades it to aspartate [194].

The same concept of *depletion* applies to more recently found inhibitors of fatty acid synthase or choline kinase [198, 199], which are in various (pre)clinical phases. Thereby, the concept of *depletion* goes always along with the risk that either the metabolites that are synthesized can be taken up from the environment or that the pathway is also essential for non-tumorigenic cells.

The concept of *normalization* is built upon the fact that some metabolic pathways such as glycolysis are also needed in healthy cells and that cancer cells display a hyperactivation of such pathways. A preclinical example for the former is 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3, which is a positive regulator of the glycolytic enzyme phosphofructokinase. Inhibition of this regulator decreases but does not inhibit glycolysis. Thus, *normalization* is sufficient to lead to proliferation inhibition, while healthy cells with lower glycolysis are unaffected [200]. Accordingly, targeting the 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 in hyper-sprouting blood vessels leads to a normalization of the blood vessels [201].

Not only the *normalization* of hyperactivated metabolic pathways leads to a therapeutic benefit, but also the reactivation of pathways that are active in healthy tissue. This is exemplified by the potency of reactivating gluconeogenesis in liver and kidney cancer. In the healthy liver glucocorticoids promote gluconeogenesis. However, in liver cancer cells, the enzymes that convert the glucocorticoids into their active form are aberrantly regulated, resulting in the insensitivity of liver cancer cells to endogenous glucocorticoids [202]. Yet, treating liver cancers with dexamethasone, which is a synthetic and active glucocorticoid, led to the re-activation of gluconeogenesis and increased therapeutic efficacy [202]. Recently, it was also shown that the re-expression of the gluconeogenic enzyme fructose 1,6 bisphosphatase 1 in renal cell carcinoma antagonized its glycolytic phenotype [203].

Examples for novel drug targets, which are in pre-clinical and clinical trials and follow the concept of *normalization* are inhibitors of the mutant form of isocitrate dehydrogenase. Point mutations in isocitrate dehydrogenase isoform 1 or isoform 2 are highly abundant in glioma, glioblastoma, and acute myeloid leukaemia. The presence of mutant isocitrate dehydrogenase in the cell leads to the production of 2-hydroxyglutarate from α -ketoglutarate, which is the product of the non-mutated isocitrate dehydrogenase reaction. Since 2-hydroxyglutarate is an endpoint metabolite that is not further converted, it rapidly accumulates in the cells and outcompetes the structurally similar α -ketoglutarate as a cofactor for α -ketoglutarate-dependent dioxygenases [204, 205]. This leads to an inhibition of the α -ketoglutarate-dependent dioxygenases and consequently to histone hypermethylation [206]. The altered methylation patterns thereby promote dedifferentiation of the tumors. Consequently, the specific inhibition of the mutant isocitrate dehydrogenase enzyme *normalizes* the methylation pattern in the tumor and leads to differentiation of tumor cells and inhibition of tumor proliferation [207-209]. Mutant isocitrate dehydrogenase inhibitors thereby constitute an ideal case of a drug target, since the mutation is only present in the tumor but not in any healthy tissue throughout the body.

In conclusion, metabolism offers a wide range of drug targets that can be exploited for cancer therapy. Yet, the current challenge is to overcome the idea that metabolism is a single and consistent entity, and to analyze cancer metabolism in the context of the tissue of origin, the (epi)genetics of the individual tumors, signaling aberrations, cancer cell heterogeneity (including cancer associate cells), and the associated microenvironment. Thus, metabolic drugs require that we move from a general standard therapy towards personalized medicine. Given the dramatic variance in tissue and specific metabolism, the possibility of a targeted delivery of drugs opens another horizon for metabolism-based therapeutic strategies.

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Figure Legends:

Figure 1: Breast cancer metabolism. A) Metabolism of triple-negative breast cancer. B) Metabolism of estrogen-positive breast cancer. *Yellow arrows* depict the main fluxes within central metabolism and the *dashed lines* indicate a down-regulation of the according metabolic pathway. The reportedly altered enzyme activities are described on the right of each panel, where *bold names* indicate an up-regulation and *condensed names* a down-regulation of the according enzymes. Abbreviations: G6P: glucose-6-phosphate, F6P: fructose-6-phosphate, F26BP: fructose-2,6-bisphosphate, F16BP: fructose-1,6-bisphosphate, GAP: glyceraldehyde-phosphate, DHAP: dihydroxyacetone-phosphate, 3PG: 3-phosphoglycerate, PEP: phosphoenol-pyruvate, 6PG: 6-phosphogluconate, R5P: ribose-5-phosphate, Pyr: pyruvate, AcCoA: acetyl-CoA, FA: fatty acids, α KG: α -ketoglutarate, OAA: oxaloacetate.

Figure 2: Liver cancer metabolism. A) Metabolism of normal hepatocytes. B) Metabolism of liver cancer. *Yellow arrows* depict the main fluxes within central metabolism and the *dashed lines* indicate a down-regulation of the according metabolic pathway. The reportedly altered enzyme activities are described on the right of each panel, where *bold names* indicate an up-regulation and *condensed names* a down-regulation of the according enzymes. Abbreviations: G6P: glucose-6-phosphate, F6P: fructose-6-phosphate, F26BP: fructose-2,6-bisphosphate, F16BP: fructose-1,6-bisphosphate, GAP: glyceraldehyde-phosphate, DHAP: dihydroxyacetone-phosphate, 3PG: 3-phosphoglycerate, PEP: phosphoenol-pyruvate, 6PG: 6-phosphogluconate, R5P: ribose-5-phosphate, Pyr: pyruvate, AcCoA: acetyl-CoA, FA: fatty acids, α KG: α -ketoglutarate, OAA: oxaloacetate.

Figure 3: Prostate metabolism at different stages of carcinogenesis. A) Metabolism of healthy prostate fibroblasts. B) Early prostate cancer metabolism C) Late stage prostate cancer metabolism. *Yellow arrows* depict the main fluxes within central metabolism and the *dashed lines* indicate a down-regulation of the according metabolic pathway. The reportedly altered enzyme activities are described on the right of each panel, where *bold names* indicate an up-regulation and *condensed names* a down-regulation of the according enzymes. Abbreviations: G6P: glucose-6-phosphate, F6P: fructose-6-phosphate, F26BP: fructose-2,6-bisphosphate, F16BP: fructose-1,6-bisphosphate, GAP: glyceraldehyde-phosphate, DHAP: dihydroxyacetone-phosphate, 3PG: 3-phosphoglycerate, PEP: phosphoenol-pyruvate, 6PG: 6-phosphogluconate, R5P: ribose-5-phosphate, Pyr: pyruvate, AcCoA: acetyl-CoA, FA: fatty acids, α KG: α -ketoglutarate, OAA: oxaloacetate.

Table Legend:

Table 1: Metabolic targets in tumor therapy. Updated and extended summary based on Galluzzi *et al.* [6] Abbreviations: PFKFB3: 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3, PFKFB4: 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 4, PKM2: pyruvate kinase muscle isozyme 2, HK: hexokinase, PGAM: phosphoglycerate mutase family, G6Pase: Glucose 6-phosphatase, PEPCK: phosphoenolpyruvate carboxykinase, CK: choline kinase, ACLY: ATP citrate lyase, FASN: fatty acid synthase, MGLL: monoacylglycerol lipase, CPT1C: carnitine palmitoyltransferase-1C, HMGCR: 3-Hydroxy-3-methylglutaryl-CoA reductase, PDK1: pyruvate dehydrogenase kinase-1, GLS1: glutaminase 1, GDH: Glutamate Dehydrogenase, IDH1/2: isocitrate dehydrogenase 1/2, MCT1: monocarboxylate transporter 1, MCT4: monocarboxylate transporter 4, MAE2: malic enzyme 2, PhGDH: phosphoglycerate dehydrogenase, ODC: ornithine decarboxylase, DHFR: dihydrofolate reductase, RNR: ribonucleotide reductase.

Target	Mode of action	Agent	Stage of development	Indication	Ref.
Glycolysis					
Glucose transporters	Depletion	Ritonavir (off-target inhibitory effects on GLUT4)	Preclinical	Multiple myeloma	[210, 211]
		WZB117	Preclinical	Lung cancer	

PFKFB3	Normalization	3PO PFK158	Preclinical Phase I	Lung, breast leukemic tumors Advanced malignancies	[212-214]
PFKFB4	Normalization	RNAi	Preclinical	Multiple cancer cell lines	[215, 216]
PKM2	Normalization	Shikonin TLN-232	Preclinical discontinued clinical trials	Various cancers Metastatic melanoma	[217-219]
HK	Depletion	2-DG, 3-BP, Lonidamine Methyl jasmonate	Discontinued clinical trials Preclinical	Advanced solid tumors Bladder and breast cancer	[220]
PGAM	Depletion	Preclinical compounds	Preclinical	Breast cancer	[221]
MCT4	Depletion	RNAi	Preclinical	Glioblastoma	[222]
Gluconeogenesis					
G6Pase, PEPCK	Normalization	Dexamethasone	Preclinical	Liver cancer	[80]
Fatty acid metabolism					
CK	Depletion	TCD-717	Approved Phase I	Advanced Solid Tumors	[199]
ACLY	Depletion	RNAi, preclinical compounds	Preclinical	Various cancers	[223-225]
FASN	Depletion	TVB-2640	Phase I	Advanced Solid Tumors	[226]
MGLL	Depletion	CK37 JZL184	Preclinical	Various cancer cells	[227, 228]
CPT1C	Depletion	RNAi	Preclinical	Lung tumor	[229]
HMGR	Depletion	Statins	Approved	Solid tumors	[230]
TCA cycle and mitochondrial metabolism					
PKM2	Normalization	DCA	Phase II	Glioblastoma; melanoma; Non-small cell lung cancer	[231, 232]
Complex I	Depletion	Metformin	Approved (not for cancer)	Metformin treatment improves outcomes in cancer patients	[233-235]
GLS1	Normalization	RNAi, preclinical compounds CB-839	Preclinical Phase I	Advanced hematologic malignancies and Solid tumors	[236, 237]
GDH	Depletion	RNAi, preclinical compounds EGCG	Preclinical	Glioblastoma cells	[238-240]
Mutant IDH1/2	Normalization	RNAi, preclinical compounds AG-221 AG-120	Preclinical Phase I Phase I	Glioma, leukemia Acute myeloid leukemia Advanced hematologic tumor and solid tumors	[241-245]
MCT1	Depletion	RNAi, preclinical compounds (AR-C155858, AR-117977), AZD3965 inhibitor	 Phase I	 Advanced cancers	[246, 247]
MAE2	Normalization	RNAi	Preclinical	Leukemia; Solid tumors	[248, 249]
Amino acid metabolism					
Asparagine	Depletion	L-asparaginase	Approved	Leukemia	[194]

PhGDH	Depletion	RNAi	Preclinical	Melanoma; Breast cancer	[42, 43]
Arginine	Depletion	Arginine deaminase conjugated to PEG	Phase II	HCC (Phase II/III); Melanoma (Phase I/II)	[250]
ODC	Depletion	DMFO	Phase II	Neuroblastoma	[251]
Nucleic acid synthesis					
DHFR	Depletion	Methotrexate	Approved	Various types of cancer	[252-254]
Nucleoside analogs	Depletion	5-FU	Approved	Solid cancer	[255]
RNR	Depletion	Gemcitabine	Approved	Pancreatic cancer	[256]

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Figure 1: Breast cancer metabolism. A) Metabolism of triple-negative breast cancers. B) Metabolism of estrogen receptor-positive breast cancers. *Yellow arrows* depict the main fluxes within central metabolism and the *dashed lines* indicate a down-regulation of the according metabolic pathway. The reportedly altered enzyme activities are described on the right of each panel, where *bold names* indicate an up-regulation and *condensed names* a down-regulation of the according enzymes. Abbreviations: G6P: glucose-6-phosphate, F6P: fructose-6-phosphate, F26BP: fructose-2,6-bisphosphate, F16BP: fructose-1,6-bisphosphate, GAP: glyceraldehyde-phosphate, DHAP: dihydroxyacetone-phosphate, 3PG: 3-phosphoglycerate, PEP: phosphoenol-pyruvate, 6PG: 6-phosphogluconate, R5P: ribose-5-phosphate, Pyr: pyruvate, AcCoA: acetyl-CoA, FA: fatty acids, αKG: α-ketoglutarate, OAA: oxaloacetate.

Figure 2: Liver cancer metabolism. A) Metabolism of normal hepatocytes. B) Metabolism of liver cancers. *Yellow arrows* depict the main fluxes within central metabolism and the *dashed lines* indicate a down-regulation of the according metabolic pathway. The reportedly altered enzyme activities are described on the *right of each panel*, where *bold names* indicate an up-regulation and *condensed names* a down-regulation of the according enzymes. Abbreviations: G6P: glucose-6-phosphate, F6P: fructose-6-phosphate, F26BP: fructose-2,6-bisphosphate, F16BP: fructose-1,6-bisphosphate, GAP: glyceraldehyde-phosphate, DHAP: dihydroxyacetone-phosphate, 3PG: 3-phosphoglycerate, PEP: phosphoenol-pyruvate, 6PG: 6-phosphogluconate, R5P: ribose-5-phosphate, Pyr: pyruvate, AcCoA: acetyl-CoA, FA: fatty acids, α KG: α -ketoglutarate, OAA: oxaloacetate.

Figure 3: Prostate metabolism at different stages of carcinogenesis. A) Metabolism of healthy prostate fibroblasts. B) Early prostate cancer metabolism C) Late stage prostate cancer metabolism. *Yellow arrows* depict the main fluxes within central metabolism and the *dashed lines* indicate a down-regulation of the according metabolic pathway. The reportedly altered enzyme activities are described on the *right of each panel*, where **bold names** indicate an up-regulation and *condensed names* a down-regulation of the according enzymes. Abbreviations: G6P: glucose-6-phosphate, F6P: fructose-6-phosphate, F26BP: fructose-2,6- bisphosphate, F16BP: fructose-1,6-bisphosphate, GAP: glyceraldehyde-phosphate, DHAP: dihydroxyacetone-phosphate, 3PG: 3- phosphoglycerate, PEP: phosphoenol-pyruvate, 6PG: 6-phosphogluconate, R5P: ribose-5-phosphate, Pyr: pyruvate, AcCoA: acetyl-CoA, FA: fatty acids, α KG: α -ketoglutarate, OAA: oxaloacetate.