HHS Public Access

Author manuscript

Int Rev Cell Mol Biol. Author manuscript; available in PMC 2020 February 03.

Published in final edited form as:

Int Rev Cell Mol Biol. 2019 ; 347: 1–26. doi:10.1016/bs.ircmb.2019.07.007.

Drugging cancer metabolism: Expectations *vs*. reality

David C. Montrose[a,*], **Lorenzo Galluzzi**[b,c,d,e,*]

[a]Department of Pathology, Renaissance School of Medicine, Stony Brook University, Stony Brook, NY, United States

[b]Department of Radiation Oncology, Weill Cornell Medical College, New York, NY, United States

[c]Sandra and Edward Meyer Cancer Center, New York, NY, United States

[d]Department of Dermatology, Yale School of Medicine, New Haven, CT, United States

[e]Université Paris Descartes/Paris V, Paris, France

Abstract

As compared to their normal counterparts, neoplastic cells exhibit a variety of metabolic changes that reflect not only genetic and epigenetic defects underlying malignant transformation, but also the nutritional and immunobiological conditions of the tumor microenvironment. Such alterations, including the so-called Warburg effect (an increase in glucose uptake largely feeding anabolic and antioxidant metabolism), have attracted considerable attention as potential targets for the development of novel anticancer therapeutics. However, very few drugs specifically conceived to target bioenergetic cancer metabolism are currently approved by regulatory agencies for use in humans. This reflects the elevated degree of heterogeneity and redundancy in the metabolic circuitries exploited by neoplastic cells from different tumors (even of the same type), as well as the resemblance of such metabolic pathways to those employed by highly proliferating normal cells. Here, we summarize the major metabolic alterations that accompany oncogenesis, the potential of targeting bioenergetic metabolism for cancer therapy, and the obstacles that still prevent the clinical translation of such a promising therapeutic paradigm.

1. Introduction

In 1924, the German physiologist and physician Otto Heinrich Warburg (1883–1970) was the first to describe the tendency of cancer cells to take up increased amounts of glucose, even in normoxic conditions (Koppenol et al., 2011; Warburg, 1924). However, the so-called Warburg effect was translated into a medical procedure in the 1980s, which is known as ^{18}F-deoxyglucose positron emission tomography (^{18}FDG-PET) (Ben-Haim and Ell, 2009). It was not until the 2000s that the bioenergetic metabolism of cancer cells began to attract widespread attention as a potential target for the development of novel therapeutic interventions (Casero et al., 2018; Galluzzi et al., 2013; Tennant et al., 2010; Vander Heiden, 2011; Zhu and Thompson, 2019). Such an intensive area of investigation has provided profound insights into the metabolic alterations that accompany malignant transformation,

*Corresponding authors: david.montrose@stonybrookmedicine.edu; deadoc80@gmail.com.

tumor progression and response to therapy (Casero et al., 2018; Galluzzi et al., 2013; Tennant et al., 2010; Vander Heiden, 2011; Zhu and Thompson, 2019). Nonetheless, very few anticancer agents currently approved by the US Food and Drug Administration (FDA) or equivalent regulatory agencies worldwide for use in humans, have been specifically conceived as modulators of bioenergetic cancer metabolism. Conversely, several conventional chemotherapeutics commonly used in the clinic, including (but not limited to) 5-fluorouracil, etoposide, doxorubicin and cisplatin, were developed based on (some degree of) selectivity for highly proliferating cells (and hence target nucleic acid metabolism or the mitotic apparatus) (Casero et al., 2018; Galluzzi et al., 2013; Tennant et al., 2010; Vander Heiden, 2011; Zhu and Thompson, 2019). At least in part, the lack of anticancer drugs targeting bioenergetic metabolism reflects some specificity issues as well as multiple misconceptions that have permeated the field over the past two decades and *de facto* hindered progress. Here, we discuss the potential of drugging bioenergetic alterations associated with malignancy, and analyze the obstacles that still prevent the full realization of such a promising therapeutic paradigm.

2. Targeting carbohydrate metabolism for cancer therapy

Despite carbohydrates being known to constitute a key source of nutrients and metabolic intermediates for cancer cells since the early 1920s, it has been only during the past 2 decades that the utilization of glucose has attracted attention as a potential target for the development of novel therapeutic regimens (Gatenby and Gillies, 2004; Hay, 2016; Vander Heiden, 2011). Glucose occupies a central role in cancer metabolism owing to its ability to feed core catabolic circuitries (*i.e.*, glycolysis potentially coupled to mitochondrial respiration) as well as several anabolic pathways, including the so-called pentose phosphate pathway (PPP) and serine synthesis (Chen and Russo, 2012; Ganapathy-Kanniappan, 2018; Li and Zhang, 2016). Altogether, these metabolic circuitries not only provide cancer cells with ATP for biochemical reactions, but also (1) building blocks to sustain cell growth and proliferation (Chen and Russo, 2012; Ganapathy-Kanniappan, 2018; Li and Zhang, 2016), (2) antioxidants to counteract the potential accumulation of cytotoxic reactive oxygen species (ROS) (Perl et al., 2011; Rodic and Vincent, 2018), and (3) at least in some settings, metabolites that are sufficient to drive oncogenesis and tumor progression (Collins et al., 2017; Yang et al., 2013).

Glucose is taken up by cells *via* dedicated glucose transporters (GLUT1–4), and first acted upon by hexokinase (HK), resulting in the generation of glucose-6-phosphate (G6P) (Hay, 2016). G6P constitutes a branching point for glucose metabolism, as it can be either isomerized into fructose-6-phosphate (F6P) to proceed towards catabolism, or fed into the PPP (Chen and Russo, 2012; Ganapathy-Kanniappan, 2018; Li and Zhang, 2016). Similarly, the glycolytic intermediate 3-phosphoglycerate can either feed glycolysis or initiate serine biosynthesis (discussed in detail below) (Hay, 2016). The ultimate step of glycolysis consists of conversion of phosphoenol-pyruvate into pyruvate by one member of the pyruvate kinase (PK) enzyme family, and pyruvate either feeds into the tricarboxylic acid (TCA) cycle or is converted to lactate by lactate dehydrogenase (LDH) for secretion (Hay, 2016). Considerable efforts have been dedicated to the investigation of each step of the glycolytic cascade in cancer cells.

Despite the presence of four GLUT genes in the human genome, GLUT1 and GLUT3 appear to be the most relevant transporters harnessed for glucose uptake by cancer cells (Ancey et al., 2018). Increased expression of GLUT transporters has been documented across multiple cancer types, generally correlating with advanced disease stage and poor outcome (Brown and Wahl, 1993; Galluzzi et al., 2017a; Grobholz et al., 1993; Jiwa et al., 2014; Koh et al., 2017; Kurahara et al., 2018; Li et al., 2016a; Zhang et al., 2019). GLUT proteins represent attractive therapeutic targets, and some research groups have investigated extensively, the possibility to develop GLUT inhibitors for the management of some human neoplasms. Most of these molecules have been shown to mediate good anticancer effects *in vitro and in vivo* (generally in xenograft tumor models established in immu-nodeficient mice) (Chan et al., 2011; Liu et al., 2012; Ojelabi et al., 2016; Siebeneicher et al., 2016). However, the majority of GLUT inhibitors are poorly isoform-specific, which poses a robust challenge for clinical development. HK is overexpressed by multiple malignancies, often correlating with severity of the disease and dismal clinical outcome (Chen et al., 2014; He et al., 2016; Huang et al., 2015; Min et al., 2013; Palmieri et al., 2009; Pudova et al., 2018; Suh et al., 2014a; Wu et al., 2017; Zhang et al., 2018). Reflecting its key role in glucose retention (glucose enters cancer cells *via* GLUTs driven by its gradient, while GLUTs are impermeant to G6P), both pharmacological and genetic interventions targeting HK in cancer cells mediate robust cytostatic and cytotoxic effects, *in vitro and in vivo* (Deng et al., 2018; Gong et al., 2014; Li et al., 2016b, 2017a,b; Thamrongwaranggoon et al., 2017; Wang et al., 2016; Yoo et al., 2019; Zhang et al., 2014a; Zhou et al., 2018). In fact, several clinical trials have been initiated to investigate the therapeutic activity of the HK inhibitor lonidamine, with mixed results (Amadori et al., 1998; Berruti et al., 2002; De Lena et al., 2001; Gebbia et al., 1997; Oudard et al., 2003; Papaldo et al., 2003; Portalone et al., 1999). However, the clinical development of lonidamine has been discontinued, at least in part reflecting its poor pharmacological specificity (Belzacq et al., 2001; Fulda et al., 2010; Ravagnan et al., 1999). Human PK exists in two major forms, M1 and M2, the latter being preferentially expressed by cancer cells (Christofk et al., 2008; Mazurek et al., 2005). The central role of PKM2 in malignant transformation and tumor progression has been repeatedly established, rendering this glycolytic enzyme another attractive target for the development of novel therapeutics (He et al., 2015; Kwon et al., 2012; Lim et al., 2012; Liu et al., 2015; Tamada et al., 2012; Wang et al., 2015a; Yuan et al., 2014; Zhan et al., 2013; Zhou et al., 2012). Consistent with this notion, pharmacological agents and genetic interventions targeting PKM2 have been shown to mediate consistent antineoplastic effects in multiple tumor models (Goldberg and Sharp, 2012; He et al., 2014; Iqbal and Bamezai, 2012; Israelsen et al., 2013; Jiang et al., 2012; Li et al., 2014; Sun et al., 2015). However, pharmacological PKM2 inhibitors generally have pleiotropic effects that are poorly reconcilable with clinical applications (Galluzzi et al., 2017b,c; Jiang et al., 2012). Thus, PKM2 inhibitors have not yet been tested clinically. In summary, while the multiple steps and several layers of regulation in glycolysis generate various potential therapeutic targets, the same complexity poses a challenge to targeting these nodes for therapeutic purposes.

Reducing dietary glucose and carbohydrate intake has been proposed as an alternative strategy to limit carbohydrate metabolism in cancer cells (Kroemer et al., 2018). Increasing dietary intake of carbohydrates has contributed to elevate the rate of obesity and associated

chronic illnesses in the US and Europe (Hochberg, 2018; Ludwig et al., 2018). Conversely, diets with low carbohydrate content, including so-called ketogenic diets have recently gained popularity in the general population as a healthy lifestyle change (Hochberg, 2018; Ludwig et al., 2018). Tolerability studies in mice proved that ketogenic diets are safe and favor beneficial changes in systemic metabolism despite unfavorable hepatic alterations (Douris et al., 2015). Recently, such a diet was shown to enhance the antitumor effects of phophoinositide-3-kinase inhibitors in rodent tumor models (Hopkins et al., 2018). Whether implementing ketogenic diets in the management of cancer patients is feasible and useful remains to be determined. Yet another sugar that has witnessed increased consumption over the last few decades is fructose, also paralleling rising obesity rates (Marriott et al., 2009; Park and Yetley, 1993). A recent study demonstrated that adminstration of high-fructose corn syrup to mice enhanced intestinal tumor growth (Goncalves et al., 2019). Although some clinical trials testing various dietary regimens in cancer patients are ongoing (Lévesque et al., 2019), further investigation into the role of dietary carbohydrates in the pathogenesis of cancer is needed, which could provide a rationale for establishing nutritional guidelines for patients.

3. Targeting amino acid utilization for cancer therapy

Besides serving as building blocks for proteins, amino acids can feed into both catabolic and anabolic metabolism, and can deliver signals that support oncogenesis (Choi and Coloff, 2019; Jewell et al., 2013). In recent years, serine and glycine have garnered considerable interest in the cancer metabolism field, largely owing to key roles in one-carbon metabolism, which is central for the synthesis of purines and other oncogenic mediators (Ducker and Rabinowitz, 2017; Locasale, 2013; Mattaini et al., 2016; Yang and Vousden, 2016). Serine is synthesized from 3-phosphoglycerate upon sequential transformation by phosphoglycerate dehydrogenase (PHGDH), phosphoserine aminotransferase 1 (PSAT1) and phosphoserine phosphatase (PSPH) (Locasale, 2013; Mattaini et al., 2016; Yang and Vousden, 2016). Of note, the reaction catalyzed by PHGDH is coupled to the conversion of NAD^+ into NADH (a substrate for mitochondrial respiration), while PSAT1 simultaneously generates α-ketoglutarate (a TCA cycle intermediate) from glutamate (Locasale, 2013; Mattaini et al., 2016; Yang and Vousden, 2016). Thus, serine synthesis is coupled to bioenergetic mitochondrial metabolism. Serine can be further processed to form glycine, a conversion that can feed into a series of complex biochemical reactions culminating with formate generation, which are cumulatively known as one-carbon metabolism (Locasale, 2013; Mattaini et al., 2016; Yang and Vousden, 2016). Formate is mainly metabolized to generate precursors for purine synthesis, which is one of the main mechanisms through which serine and glycine support cancer cell proliferation (Locasale, 2013; Mattaini et al., 2016; Yang and Vousden, 2016).

Intensive efforts have been devoted to the development of strategies to block the synthesis of serine in neoplastic cells. Importantly, the levels of these amino acids are elevated in several cancers, as is the expression of their respective biosynthetic enzymes, lending further support to the therapeutic potential of targeting these pathways in cancer (DeNicola et al., 2015; Hirayama et al., 2009; Locasale et al., 2011; Possemato et al., 2011; Vie et al., 2008; Zhang et al., 2017). Early work demonstrating that PHGDH silencing impairs cancer cell

proliferation provided strong rationale for the development of PHGDH inhibitors (Locasale et al., 2011; Possemato et al., 2011). First generation PHGDH inhibitors developed by the Cantley and Sabatini groups were able to reduce serine production and limit cancer cell proliferation, both *in vitro and in vivo* (Mullarky et al., 2016; Pacold et al., 2016). Subsequently, an allosteric inhibitor of PHGDH was also developed, displaying robust anticancer effects in multiple tumor models (Wang et al., 2017). Although these agents have shown promise *in vitro and in vivo*, their development is still in its infancy and it is hard to predict whether these or next generation compounds will have clinical utility.

One-carbon metabolism can also be targeted at reactions downstream, including those mediated by methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 2, methenyltetrahydrofolate cyclohydrolase (MTHFD2) and serine hydroxymethyltransferase 1 (SHMT1) or SHMT2. Thus, deletion of MTHFD2 in human colorectal carcinoma HCT-116 cells slowed tumor growth in xenograft models, an effect that could be further enhanced by SHMT1 deletion, while SHMT1 deletion alone had no effect on tumor growth (Ducker et al., 2016). Of note, the need to delete both enzymes for maximal efficacy reflected the reversal of cytosolic one-carbon flux when the mitochondrial folate pathway was disrupted (Ducker et al., 2016). These findings highlight the adaptive nature of cancer cell metabolism and the accompanying complexity of targeting these pathways for cancer treatment. Thus, it is possible that combinatorial strategies may be required for effectively targeting one-carbon metabolism (and perhaps other metabolic circuitries) for clinical applications (Gustafsson et al., 2017; Ju et al., 2018; Ma et al., 2017).

Additional amino acids have attracted attention from the research community over the past 2 decades, including glutamine and asparagine. Each of these amino acids play a distinct but interrelated role in cell metabolism, providing rational targets for anticancer therapy. Glutamine, a precursor for glutamate, is key for the generation of glutathione and serves as a substrate for the production of TCA cycle intermediates (in support of cell proliferation) (Wise and Thompson, 2010). Glutamine-targeting agents include inhibitors of glutaminase (GLS), the enzyme that converts glutamine to glutamate, as well as agents targeting glutamine transport (Li et al., 2019; Schulte et al., 2018; Song et al., 2018; Ye et al., 2018). In fact, the glutaminase inhibitor CB-839 is being evaluated in patients affected by various cancers (source: http://www.clinicaltrials.gov). The key role of asparagine in malignant transformation and tumor progression is well-recognized, as recombinant variants of asparaginase (ASPG), the enzyme that converts asparagine to aspartic acid, have been used extensively as part of therapeutic regimens for acute lymphoblastic leukemia (Barr et al., 1992; Ertel et al., 1979; Pieters et al., 2011; Sutow et al., 1971). With that being said, it seems that asparagine synthetase—the enzyme that catalyzes the reverse conversion of aspartic acid into asparagine—may also constitute a therapeutic target, especially in asparaginase resistant cancers (Gutierrez et al., 2006; Yu et al., 2016). Additional work is required to elucidate this possibility.

It should be noted that cancer cells obtain amino acids (and other nutrients) not only from the extracellular milieu or via endogenous biosynthetic pathways, but also through autophagy (Galluzzi et al., 2017a, 2018; Rybstein et al., 2018). Autophagy, an evolutionary conserved response that recycles disposable cytosolic material *via* lysosomal degradation

(Galluzzi et al., 2017a; Morselli et al., 2010), is often upregulated in established cancers, reflecting not only nutritional needs, but also the relatively harsh conditions of the tumor microenvironment (Galluzzi et al., 2015; Sica et al., 2015). Moreover, amino acid levels are tightly linked to autophagic responses, so that limiting amino acid availability generally promoted autophagy activation, resulting in enhanced resistance to therapy (Efeyan et al., 2013; Jewell et al., 2013; Martinez-Outschoorn et al., 2017). Targeting autophagy for cancer therapy is an active area of investigation with multiple obstacles, including not only the limited specificity of currently available autophagy inhibitors, but also the critical role of autophagy in non-transformed cells (Galluzzi et al., 2017b).

Many of the amino acids under investigation as therapeutic targets for cancer therapy are non-essential, meaning that they are available from dietary sources and can be synthesized endogenously. In fact, several studies have demonstrated the importance of exogenous amino acid sources for cancer cell proliferation, *in vitro and in vivo* (Gao et al., 2018; Labuschagne et al., 2014; Maddocks et al., 2013, 2017). Strategies to reduce exogenous amino acid availability include inhibitors of amino acids transporters, such as inhibitors of solute carrier family 1 member 5 (SLC1A5, best known as ASCT2), and dietary interventions. The former approach has shown some promise in pre-clinical settings (Ndaru et al., 2019; Schulte et al., 2018; Ye et al., 2018). However, since ASCT2 controls the uptake of multiple amino acids, specificity is an issue (Ndaru et al., 2019; Schulte et al., 2018; Ye et al., 2018). The latter approach may also be challenging, as it will prove difficult to specifically reduce the dietary intake of select amino acids. That said, it has been proposed that a low-protein diet might be advantageous for cancer patients (Kerr et al., 2017; Logan and Bourassa, 2018; Yin et al., 2018), a possibility that remains to be fully explored.

4. Targeting lipid metabolism for cancer therapy

Lipids, which have historically been considered as mere structural components of cell membranes, are now widely considered as key nutrients and signal transducers that play a major role in oncogenic pathways (Hannun and Obeid, 2018; Loew et al., 2019; Wang et al., 2018).

Fatty acids (FAs) can be either obtained exogenously (from dietary sources) or be endogenously synthesized. At odds with normal cells, which generally take up FAs from the microenvironment, embryonic and cancer cells favor FA biosynthesis (Chakravarthy et al., 2005; Chirala et al., 2003; Maningat et al., 2009; Pizer et al., 1997). The first, rate-limiting step in FA synthesis is catalyzed by fatty acid synthase (FASN), which converts TCA cycle-derived acetyl-CoA into palmitate *via* a NADPH-dependent reaction (Jones and Infante, 2015). FASN plays a well-recognized role in oncogenesis and tumor progression, as first suggested by the fact that FASN levels are increased in both the circulation and neoplastic lesions of patients with cancer (Alo et al., 2007; Cai et al., 2015; Long et al., 2014; Walter et al., 2009; Witkiewicz et al., 2008). These observations drove the development of FASN inhibitors for anticancer applications, some of which demonstrated good preclinical activity (often in the context of significant off-target effects) (Flavin et al., 2010; Menendez and Lupu, 2017; Schcolnik-Cabrera et al., 2018; Zadra et al., 2019; Zhou et al., 2003). These agents, which are generally believed to operate by disrupting membrane synthesis, are being

tested in multiple clinical trials, including a completed Phase I study (). To the best of our knowledge however, the results of this study have not yet been revealed. Interestingly, proton pump inhibitors are being repurposed for cancer therapy following the demonstration that they effectively inhibit FASN (Fako et al., 2015). Supporting the clinical utility of this approach, proton pump inhibitors combined with standard-of-care chemotherapy prolonged survival in cohorts of patients with breast cancer (Fako et al., 2015; Wang et al., 2015b), and clinical trials are ongoing to further test this therapeutic paradigm (source: http://www.clinicaltrials.gov).

Cancer cells also employ FAs as nutrients for ATP production *via* fatty acid oxidation (Corbet and Feron, 2017). This biochemical cascade begins with the esterification of FAs into FA esters by acyl-CoA synthetase long chain family member 1 (ACSL1), followed by the conversion of FA esters into acylcarnitine esters, a carnitine-dependent reaction catalyzed by carnitine palmitoyltransferase 1A (CPT1A) (Casals et al., 2016; Corbet and Feron, 2017; Saavedra-Garcia et al., 2018; Schooneman et al., 2013). Acylcarnitine esters can enter the mitochondrial matrix, where carnitine is removed by CPT2 to form acyl-CoA, and the latter feeds into the TCA cycle for energy production (Casals et al., 2016; Corbet and Feron, 2017; Saavedra-Garcia et al., 2018; Schooneman et al., 2013). The key reaction in FAO is catalyzed by CPT1A, drawing attention to this enzyme as a possible target for cancer therapy (Corbet and Feron, 2017). Thus, CPT1A inhibitors such as etomoxir and perhexiline have demonstrated preclinical activity in models of leukemia and glioblastoma, as well as breast and colorectal cancer (Estan et al., 2014; Foster et al., 1988; Hernlund et al., 2008; Pike et al., 2011; Ramu et al., 1984; Samudio et al., 2010; Thupari et al., 2001; Tirado-Velez et al., 2012; Vella et al., 2015). However, none of these agents have reached clinical development so far (source: http://www.clinicaltrials.gov).

Arachidonic acid (AA) is a type of FA which has attracted considerable attention for the development of anticancer agents, reflecting the major oncogenic functions of AA-derived lipids, including prostaglandins (PGs). Following the actions of phospholipases on membrane phospholipids, AA is transformed by cyclooxygenase 1 (COX-1) or COX-2 to form PGG_2, further followed by conversion to PGH_2 (Dubois et al., 1998; Simmons et al., 2004). PGH_2 can subsequently be converted to multiple bioactive PGs by selective PG synthases (Dubois et al., 1998; Simmons et al., 2004). In this context, PGE_2 production has attracted considerable attention as a potential target for therapeutic interventions. Indeed, prostaglandin E synthase (PTGES) is overexpressed in cancers of the lung, colon, breast, brain and penis, generally correlating with elevated COX-2 expression (Cook et al., 2016; Golijanin et al., 2004; Mehrotra et al., 2006; Yoshimatsu et al., 2001a,b). Similarly, the PGE_2-catabolizing enzyme 15-hydroxyprostaglandin dehydrogenase (HPGD, also known as 15-PGDH) is commonly downregulated in the same tumors, indicating a two-fold mechanism by which cancers maintain elevated PGE_2 levels (Backlund et al., 2005; Ding et al., 2005; Hughes et al., 2008; Wolf et al., 2006; Yan et al., 2004). Moreover, PGE_2 synthesis can be boosted by caspase 3 (CASP3) activation, providing a mechanism for dying cancer cells to support the growth of their chemo- or radioresistant neighbors (Galluzzi et al., 2012a,b; Huang et al., 2011).

Pharmacological approaches to reduce PG production have been used clinically for decades. In particular, non-steroidal anti-inflammatory drugs (NSAIDs) were originally formulated to reduce pain and inflammation, largely reflecting the non-selective inhibition of COX-1 and COX-2 (Dubois et al., 1998; Simmons et al., 2004). Although clinically useful for their intended purpose, these drugs cause gastric and enteric complications in animals and a subset of individuals (Bjarnason et al., 1993; Halter et al., 2001; Sigthorsson et al., 2002; Thiefin and Beaugerie, 2005; Wallace and Devchand, 2005; Whittle, 2004), calling for the development of next-generation NSAIDs selectively targeting COX-2 (Everts et al., 2000). Second-generation NSAIDs were associated with reduced gastrointestinal events, but their use was rapidly linked with adverse cardiovascular effects (Bombardier et al., 2000; Silverstein et al., 2000).

In addition to their anti-inflammatory properties, NSAIDs have strong chemopreventive effects. Work in rodents demonstrated the chemopreventive efficacy of the selective COX-2 inhibitor celecoxib on intestinal tumorigenesis (Ignatenko et al., 2008; Jacoby et al., 2000; Montrose et al., 2016). Moreover, NSAID users exhibited lower propensities to develop both sporadic and genetically predisposed adenomas (Bertagnolli et al., 2006; Steinbach et al., 2000). The utility of other coxibs and sulindac (yet another NSAID) for the chemoprevention of gastrointestinal tumors has also been demonstrated in prospective clinical trials (Baron et al., 2006; Giardiello et al., 2002). Conversely, the chemopreventive efficacy of aspirin—which also operates as a COX-1/COX-2 inhibitor—appears to exhibit a considerable degree of variability with tumor type (Bardia et al., 2007; Benamouzig et al., 2010; Burn et al., 2011; Cook et al., 2005; Liao et al., 2012).

In spite of their utility as chemopreventive agents, COX inhibitors are impractical to use in the general population due to gastrointestinal and cardiovascular toxicities, as outlined above. These adverse effects are on-target, meaning that they result from COX inhibition and a consequent drop in PG bioavailability. To circumvent this problem, efforts have been redirected to the development of specific inhibitors of PGE_2 synthesis. Work in rodents demonstrated that *Ptges* deletion reduced intestinal and mammary tumor growth (Howe et al., 2013; Nakanishi et al., 2008; Sasaki et al., 2012). However, although pharmacological inhibitors of PTGES have been developed, their utility in humans for cancer prevention or treatment has yet to be demonstrated (Brenneis et al., 2006).

Sphingolipids represent another major class of lipids with central roles in malignant transformation and tumor progression (Bartke and Hannun, 2009; Hannun and Obeid, 2018). Sphingomyelin, an abundant sphingolipid of cell membranes, can be converted by sphingomyelinase into ceramide, a lipid second messenger with multipronged cellular effects (Bieberich, 2008). In turn, ceramide can be converted to sphingosine-1-phosphate (S1P) through the sequential actions of ceramidase and sphingosine kinases (Hannun and Obeid, 2008). Ceramide, sphingosine and S1P have all been involved in oncogenesis or tumor progression, and the enzymes responsible for their synthesis are upregulated in multiple cancer types (Furuya et al., 2011; Hannun and Obeid, 2018; Ogretmen, 2018). For example, ceramidase is elevated in leukemia as well as prostate and colorectal cancer (Beckham et al., 2013; Cheng et al., 2013; Garcia-Barros et al., 2016; Seelan et al., 2000; Tan et al., 2016). Consistent with these observations, inhibition of ceramidases caused

cancer cell death and delayed tumor growth in xenograft models (Mahdy et al., 2009; Selzner et al., 2001; Vijayan et al., 2019). The apoptotic effects of ceramidase inhibition largely result from intracellular ceramide accumulation, ultimately driving mitochondrial membrane permeabilization and downstream CASP3 activation (Galluzzi et al., 2010; Susin et al., 1997; Tait and Green, 2010). Accordingly, several studies have shown that supplementing rodent diets with sphingomyelin reduces intestinal tumor development (Dillehay et al., 1994; Schmelz et al., 1996). These preclinical results suggest that inhibitors of ceramidase may constitute effective anticancer agents for clinical applications, a possibility that remains to be tested.

S1P is a highly bioactive mediator known for its roles in normal physiology and pathology. Upon binding to one of its cognate receptors, S1P regulates angiogenesis, vascular permeability and physiological lymphocyte trafficking (McVerry and Garcia, 2005; Montrose et al., 2013; Pappu et al., 2007; Rivera et al., 2008; Wang and Dudek, 2009). Consistent with the importance of this signaling pathway, an S1P receptor modulator (i.e., fingolimod) has been approved by the US FDA for the management of multiple sclerosis, and similar compounds are in clinical development for the treatment of ulcerative colitis (Brinkmann et al., 2010; Sandborn et al., 2016). The potential utility of targeting this pathway for cancer treatment has also been demonstrated. Genetic deletion of *Sphk1* (coding for sphingosine kinase 1) reduced tumor burden in a murine model of intestinal neoplasia (Furuya et al., 2017a; Kohno et al., 2006). Interestingly, macrophages have been suggested as an important source for sphingosine kinase activity in the microenvironment of colorectal carcinoma (Furuya et al., 2017b). Moreover, the ability of a SPHK1 inhibitor to suppress colitisassociated tumorigenesis has been attributed to disruption of specific immune cell populations (Chumanevich et al., 2010). Other cancer types in which SPHK1 might constitute a relevant target for the development of therapeutic agents include glioma as well as breast and prostate carcinoma (Geffken and Spiegel, 2018; Kapitonov et al., 2009; Pchejetski et al., 2011; Shimizu et al., 2018; Zhang et al., 2014b). The existence of FDA-approved modulators of S1P receptors may facilitate the development of anticancer regimens based on these molecules.

5. Obstacles to drugging bioenergetic metabolism for therapeutic purposes

Despite the enthusiasm raised by the possibility of drugging bioenergetic metabolism as a novel pharmacological approach against neoplasia, such a therapeutic paradigm remains largely unrealized for several reasons. First, the bioenergetic circuitries harnessed by neoplastic cells to thrive despite the harsh conditions that generally characterize the tumor microenvironment (*e.g.*, the Warburg effect) exhibit considerable overlap with the bioenergetic pathways employed by non-malignant cells that engage in rapid proliferative responses physiologically, such as T lymphocytes expanding in response to an antigenic challenge or the wound healing response (Buck et al., 2015, 2017; Lisowska et al., 2018; Ma et al., 2017; Rodrigues et al., 2019; Slominski et al., 2018). Thus, the systemic administration of glycolysis inhibitors such as 2-deoxy-*D*-glucose at pharmacologically meaningful doses has the potential to generate off-target effects that may limit the ability of

the immune system to control disease or repair injuries. In line with this notion, early clinical trials testing 2-deoxy-D-glucose plus docetaxel or radiation therapy in patients with advanced solid tumors demonstrate that the drug is well tolerated but fails to provide clinical benefits (Raez et al., 2013; Singh et al., 2005). Second, accumulating preclinical and clinical data suggest that malignant cells acquire metabolic alterations that are highly heterogeneous. This heterogeneity can occur across (1) cancer types (Camelo and Le, 2018; Crippa et al., 2017; Goodwin et al., 2017; Nguyen and Le, 2018), (2) patients with the same type of neoplasm (Cappelletti et al., 2017; Kim et al., 2015; Quinones and Le, 2018), (3) lesions at different sites within the same individual (*e.g.*, primary tumor *vs.* metastatic) (Guha et al., 2018; Kidd and Grigsby, 2008; Lehuede et al., 2016; Pahk et al., 2018), and (4) in different areas of the very same lesion (Carmona-Fontaine et al., 2017; Feichtinger et al., 2011; Yoshida, 2015). The ultimate metabolic configuration of a transformed cell indeed depends on genetic and epigenetic features that are not necessarily shared with other tumors of the same type, such as the loss of the oncosuppressor tumor protein 53 (TP53) (Vander Linden and Corbet, 2019). Moreover, the precise microenvironment in which a malignant lesion evolves has a major impact on which metabolic circuitries can be harnessed for survival and proliferation (Suh et al., 2014b; Yoshida, 2015). Additionally, cancer cells evolve at a rapid pace under microenvironmental pressure (including metabolic and immunological cues), which drives a considerable degree of diversification, even within the same lesion (Suh et al., 2014b; Vitale et al., 2019; Yoshida, 2015). These observations imply that drugging a specific metabolic circuitry associated with malignancy may ultimately be efficient only on a fraction of cancer cells, *de facto* operating as selective pressure and favoring the rapid emergence of resistant cells. Third, the metabolic changes that enable the malignant phenotype are not a self-standing hallmark of cancer, as proposed by many investigators (Hanahan and Weinberg, 2011). Rather, bioenergetic metabolism is finely coupled to (and hence indiscernible from) all other functions of cancer cells, meaning that all phenotypical, biological and immunological manifestations of malignancy are linked to bioenergetic metabolism, either quite directly (*e.g.*, a high proliferation rate requires robust anabolism in support of novel biomass generation) or less so (*e.g.*, a high ATP content facilitates the perception of cell death as immunogenic) (Galluzzi et al., 2017d; Michaud et al., 2011). This implies that any biological, immunological or therapeutic challenge faced by malignant cells alters their metabolism, often in ways that remain to be elucidated.

Taken together, these observations suggest that the development of efficient strategies to drug bioenergetic metabolism for therapeutic purposes calls for the identification of metabolic alterations that are (1) as specific to cancer (over normal) cells as possible, and (2) as common amongst cancer cells as possible (at least within individual patients). Moreover, it will be critical to keep under attentive consideration the fact that any therapeutic agent administered to cancer patients alters the bioenergetic configurations of cancer cells, potentially exposing (or concealing) susceptibilities (Michels et al., 2013; Obrist et al., 2018).

6. Concluding remarks

In summary, the bioenergetic machinery of malignant cells stands out as a promising source of targets for the development of novel therapeutic agents. However, drugging a cellular

function as conserved and flexible as bioenergetic metabolism remains challenging. In this context, considerable efforts will have to be dedicated not only to solving the specificity issues discussed here above, but also to obtaining in-depth knowledge on the interactions between bioenergetic metabolism in cancer cells and (1) currently employed anticancer agents, and (2) nutritional cues. Accumulating preclinical and clinical data indicates indeed that nutrition has a major impact on multiple steps of the oncogenic process (Galluzzi et al., 2017c; Goncalves et al., 2019; Hopkins et al., 2018; Kroemer et al., 2018; L evesque et al., 2019; Ngo et al., 2019), calling for an attentive re-evaluation of dietary recommendations given to cancer patients. In spite of persisting obstacles, it is tempting to surmise that (but only the future will tell whether) targeting cancer metabolism with pharmacological agents or nutritional interventions will soon become a clinical reality.

Acknowledgments

D.C.M. is supported by the NIH (K22CA226033) and a grant from the Prevent Cancer Foundation. L.G. is supported by a Breakthrough Level 2 grant from the US Department of Defense (DoD), Breast Cancer Research Program (BRCP) [#BC180476P1], by a startup grant from the Dept. of Radiation Oncology at Weill Cornell Medicine (New York, US), by industrial collaborations with Lytix (Oslo, Norway) and Phosplatin (New York, US), and by donations from Phosplatin (New York, US), the Luke Heller TECPR2 Foundation (Boston, US) and Sotio a.s. (Prague, Czech Republic).

References

Alo PL, et al., 2007 Immunohistochemical expression and prognostic significance of fatty acid synthase in pancreatic carcinoma. Anticancer Res. 27, 2523–2527. [PubMed: 17695548]

Amadori D, et al., 1998 Modulating effect of lonidamine on response to doxorubicin in metastatic breast cancer patients: results from a multicenter prospective randomized trial. Breast Cancer Res. Treat 49, 209–217. [PubMed: 9776504]

Ancey PB, et al., 2018 Glucose transporters in cancer—from tumor cells to the tumor microenvironment. FEBS J. 285, 2926–2943. [PubMed: 29893496]

Backlund MG, et al., 2005 15-Hydroxyprostaglandin dehydrogenase is down-regulated in colorectal cancer. J. Biol. Chem 280, 3217–3223. [PubMed: 15542609]

Bardia A, et al., 2007 Association of aspirin and nonaspirin nonsteroidal anti-inflammatory drugs with cancer incidence and mortality. J. Natl. Cancer Inst 99, 881–889. [PubMed: 17551148]

Baron JA, et al., 2006 A randomized trial of rofecoxib for the chemoprevention of colorectal adenomas. Gastroenterology 131, 1674–1682. [PubMed: 17087947]

Barr RD, et al., 1992 Management of children with acute lymphoblastic leukemia by the Dana-Farber Cancer Institute protocols. An update of the Ontario experience. Am. J. Pediatr. Hematol. Oncol 14, 136–139. [PubMed: 1530118]

Bartke N, Hannun YA, 2009 Bioactive sphingolipids: metabolism and function. J. Lipid Res 50 (Suppl), S91–S96. [PubMed: 19017611]

Beckham TH, et al., 2013 Acid ceramidase induces sphingosine kinase 1/S1P receptor 2-mediated activation of oncogenic Akt signaling. Oncogenesis 2, e49. [PubMed: 23732709]

Belzacq AS, et al., 2001 Adenine nucleotide translocator mediates the mitochondrial membrane permeabilization induced by lonidamine, arsenite and CD437. Oncogene 20, 7579–7587. [PubMed: 11753636]

Benamouzig R, et al., 2010 Cyclooxygenase-2 expression and recurrence of colorectal adenomas: effect of aspirin chemoprevention. Gut 59, 622–629. [PubMed: 20427397]

Ben-Haim S, Ell P, 2009 18F-FDG PET and PET/CT in the evaluation of cancer treatment response. J. Nucl. Med 50, 88–99. [PubMed: 19139187]

Berruti A, et al., 2002 Time to progression in metastatic breast cancer patients treated with epirubicin is not improved by the addition of either cisplatin or lonidamine: final results of a phase III study with a factorial design. J. Clin. Oncol 20, 4150–4159. [PubMed: 12377958]

Bertagnolli MM, et al., 2006 Celecoxib for the prevention of sporadic colorectal adenomas. N. Engl. J. Med 355, 873–884. [PubMed: 16943400]

Bieberich E, 2008 Ceramide signaling in cancer and stem cells. Futur. Lipidol 3, 273–300.

Bjarnason I, et al., 1993 Side effects of nonsteroidal anti-inflammatory drugs on the small and large intestine in humans. Gastroenterology 104, 1832–1847. [PubMed: 8500743]

Bombardier C, et al., 2000 Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. N. Engl. J. Med 343, 1520–1528. 1522 p following 1528. [PubMed: 11087881]

Brenneis C, et al., 2006 Inhibition of prostaglandin E2 synthesis by SC-560 is independent of cyclooxygenase 1 inhibition. FASEB J. 20, 1352–1360. [PubMed: 16816110]

Brinkmann V, et al., 2010 Fingolimod (FTY720): discovery and development of an oral drug to treat multiple sclerosis. Nat. Rev. Drug Discov 9, 883–897. [PubMed: 21031003]

Brown RS, Wahl RL, 1993 Overexpression of Glut-1 glucose transporter in human breast cancer. An immunohistochemical study. Cancer 72, 2979–2985. [PubMed: 8221565]

Buck MD, et al., 2015 T cell metabolism drives immunity. J. Exp. Med 212, 1345–1360. [PubMed: 26261266]

Buck MD, et al., 2017 Metabolic instruction of immunity. Cell 169, 570–586. [PubMed: 28475890]

Burn J, et al., 2011 Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. Lancet 378, 2081–2087. [PubMed: 22036019]

Cai Y, et al., 2015 Expressions of fatty acid synthase and HER2 are correlated with poor prognosis of ovarian cancer. Med. Oncol 32, 391. [PubMed: 25433947]

Camelo F, Le A, 2018 The intricate metabolism of pancreatic cancers. Adv. Exp. Med. Biol 1063, 73–81. [PubMed: 29946776]

Cappelletti V, et al., 2017 Metabolic footprints and molecular subtypes in breast cancer. Dis. Markers 2017, 7687851. [PubMed: 29434411]

Carmona-Fontaine C, et al., 2017 Metabolic origins of spatial organization in the tumor microenvironment. Proc. Natl. Acad. Sci. U.S.A 114, 2934–2939. [PubMed: 28246332]

Casals N, et al., 2016 Carnitine palmitoyltransferase 1C: from cognition to cancer. Prog. Lipid Res 61, 134–148. [PubMed: 26708865]

Casero RA Jr., et al., 2018 Polyamine metabolism and cancer: treatments, challenges and opportunities. Nat. Rev. Cancer 18, 681–695. [PubMed: 30181570]

Chakravarthy MV, et al., 2005 “New” hepatic fat activates PPARalpha to maintain glucose, lipid, and cholesterol homeostasis. Cell Metab. 1, 309–322. [PubMed: 16054078]

Chan DA, et al., 2011 Targeting GLUT1 and the Warburg effect in renal cell carcinoma by chemical synthetic lethality. Sci. Transl. Med 3, 94ra70.

Chen JQ, Russo J, 2012 Dysregulation of glucose transport, glycolysis, TCA cycle and glutaminolysis by oncogenes and tumor suppressors in cancer cells. Biochim. Biophys. Acta 1826, 370–384. [PubMed: 22750268]

Chen J, et al., 2014 Hexokinase 2 overexpression promotes the proliferation and survival of laryngeal squamous cell carcinoma. Tumour Biol. 35, 3743–3753. [PubMed: 24363061]

Cheng JC, et al., 2013 Radiation-induced acid ceramidase confers prostate cancer resistance and tumor relapse. J. Clin. Invest 123, 4344–4358. [PubMed: 24091326]

Chirala SS, et al., 2003 Fatty acid synthesis is essential in embryonic development: fatty acid synthase null mutants and most of the heterozygotes die in utero. Proc. Natl. Acad. Sci. U.S.A 100, 6358–6363. [PubMed: 12738878]

Choi BH, Coloff JL, 2019 The diverse functions of non-essential amino acids in cancer. Cancers (Basel) 11 (5), E675. [PubMed: 31096630]

Christofk HR, et al., 2008 The M2 splice isoform of pyruvate kinase is important for cancer metabolism and tumour growth. Nature 452, 230–233. [PubMed: 18337823]

Chumanevich AA, et al., 2010 Suppression of colitis-driven colon cancer in mice by a novel small molecule inhibitor of sphingosine kinase. Carcinogenesis 31, 1787–1793. [PubMed: 20688834]

Collins RRJ, et al., 2017 Oncometabolites: a new paradigm for oncology, metabolism, and the clinical laboratory. Clin. Chem 63, 1812–1820. [PubMed: 29038145]

Cook NR, et al., 2005 Low-dose aspirin in the primary prevention of cancer: the women's health study: a randomized controlled trial. JAMA 294, 47–55. [PubMed: 15998890]

Cook PJ, et al., 2016 Cox-2-derived PGE2 induces Id1-dependent radiation resistance and self-renewal in experimental glioblastoma. Neuro-Oncology 18, 1379–1389. [PubMed: 27022132]

Corbet C, Feron O, 2017 Emerging roles of lipid metabolism in cancer progression. Curr.Opin. Clin. Nutr. Metab. Care 20, 254–260. [PubMed: 28403011]

Crippa S, et al., 2017 Mutant CTNNB1 and histological heterogeneity define metabolic subtypes of hepatoblastoma. EMBO Mol. Med 9, 1589–1604. [PubMed: 28923827]

De Lena M, et al., 2001 Paclitaxel, cisplatin and lonidamine in advanced ovarian cancer. A phase II study. Eur. J. Cancer 37, 364–368. [PubMed: 11239758]

Deng Y, et al., 2018 Overexpression of miR-202 resensitizes imatinib resistant chronic myeloid leukemia cells through targetting Hexokinase 2. Biosci. Rep 38 (3), BSR20171383. [PubMed: 29559564]

DeNicola GM, et al., 2015 NRF2 regulates serine biosynthesis in non-small cell lung cancer. Nat. Genet 47, 1475–1481. [PubMed: 26482881]

Dillehay DL, et al., 1994 Dietary sphingomyelin inhibits 1,2-dimethylhydrazine-induced colon cancer in CF1 mice. J. Nutr 124, 615–620. [PubMed: 8169652]

Ding Y, et al., 2005 NAD+-linked 15-hydroxyprostaglandin dehydrogenase (15-PGDH) behaves as a tumor suppressor in lung cancer. Carcinogenesis 26, 65–72. [PubMed: 15358636]

Douris N, et al., 2015 Adaptive changes in amino acid metabolism permit normal longevity in mice consuming a low-carbohydrate ketogenic diet. Biochim. Biophys. Acta 1852, 2056–2065. [PubMed: 26170063]

Dubois RN, et al., 1998 Cyclooxygenase in biology and disease. FASEB J. 12, 1063–1073. [PubMed: 9737710]

Ducker GS, Rabinowitz JD, 2017 One-carbon metabolism in health and disease. CellMetab. 25, 27–42.

Ducker GS, et al., 2016 Reversal of cytosolic one-carbon flux compensates for loss of the mitochondrial folate pathway. Cell Metab. 23, 1140–1153. [PubMed: 27211901]

Efeyan A, et al., 2013 Regulation of mTORC1 by the Rag GTPases is necessary for neonatal autophagy and survival. Nature 493, 679–683. [PubMed: 23263183]

Ertel IJ, et al., 1979 Effective dose of L-asparaginase for induction of remission in previously treated children with acute lymphocytic leukemia: a report from Childrens Cancer Study Group. Cancer Res. 39, 3893–3896. [PubMed: 383278]

Estan MC, et al., 2014 Apoptotic efficacy of etomoxir in human acute myeloid leukemia cells. Cooperation with arsenic trioxide and glycolytic inhibitors, and regulation by oxidative stress and protein kinase activities. PLoS One 9 e115250. [PubMed: 25506699]

Everts B, et al., 2000 COX-2-specific inhibitors—the emergence of a new class of analgesic and anti-inflammatory drugs. Clin. Rheumatol 19, 331–343. [PubMed: 11055820]

Fako VE, et al., 2015 Repositioning proton pump inhibitors as anticancer drugs by targeting the thioesterase domain of human fatty acid synthase. J. Med. Chem 58, 778–784. [PubMed: 25513712]

Feichtinger RG, et al., 2011 Heterogeneity of mitochondrial energy metabolism in classical triphasic Wilms' tumor. Front. Biosci. (Elite Ed.) 3, 187–193. [PubMed: 21196297]

Flavin R, et al., 2010 Fatty acid synthase as a potential therapeutic target in cancer. Future Oncol. 6, 551–562. [PubMed: 20373869]

Foster BJ, et al., 1988 Modulation of induced resistance to adriamycin in two human breast cancer cell lines with tamoxifen or perhexiline maleate. Cancer Chemother. Pharmacol 22, 147–152. [PubMed: 3409446]

Fulda S, et al., 2010 Targeting mitochondria for cancer therapy. Nat. Rev. Drug Discov 9, 447–464. [PubMed: 20467424]

Furuya H, et al., 2011 Sphingolipids in cancer. Cancer Metastasis Rev. 30, 567–576. [PubMed: 22005951]

Furuya H, et al., 2017a Sphingosine kinase 1 expression enhances colon tumor growth. J. Transl. Med 15, 120. [PubMed: 28583134]

Furuya H, et al., 2017b Sphingosine Kinase 1 expression in peritoneal macrophages is required for colon carcinogenesis. Carcinogenesis 38, 1218–1227. [PubMed: 29028945]

Galluzzi L, et al., 2010 miR-181a and miR-630 regulate cisplatin-induced cancer cell death. Cancer Res. 70, 1793–1803. [PubMed: 20145152]

Galluzzi L, et al., 2012a Caspase-3 and prostaglandins signal for tumor regrowth in cancer therapy. Oncogene 31, 2805–2808. [PubMed: 21963852]

Galluzzi L, et al., 2012b Non-apoptotic functions of apoptosis-regulatory proteins. EMBO Rep. 13, 322–330. [PubMed: 22402666]

Galluzzi L, et al., 2013 Metabolic targets for cancer therapy. Nat. Rev. Drug Discov 12, 829–846. [PubMed: 24113830]

Galluzzi L, et al., 2015 Autophagy in malignant transformation and cancer progression. EMBO J. 34, 856–880. [PubMed: 25712477]

Galluzzi L, et al., 2017a Molecular definitions of autophagy and related processes. EMBO J. 36, 1811–1836. [PubMed: 28596378]

Galluzzi L, et al., 2017b Pharmacological modulation of autophagy: therapeutic potential and persisting obstacles. Nat. Rev. Drug Discov 16, 487–511. [PubMed: 28529316]

Galluzzi L, et al., 2017c Activating autophagy to potentiate immunogenic chemotherapy and radiation therapy. Nat. Rev. Clin. Oncol 14, 247–258. [PubMed: 27845767]

Galluzzi L, et al., 2017d Immunogenic cell death in cancer and infectious disease. Nat. Rev. Immunol 17, 97–111. [PubMed: 27748397]

Galluzzi L, et al., 2018 Linking cellular stress responses to systemic homeostasis. Nat. Rev. Mol. Cell Biol 19, 731–745. [PubMed: 30305710]

Ganapathy-Kanniappan S, 2018 Molecular intricacies of aerobic glycolysis in cancer: current insights into the classic metabolic phenotype. Crit. Rev. Biochem. Mol. Biol 53, 667–682. [PubMed: 30668176]

Gao X, et al., 2018 Serine availability influences mitochondrial dynamics and function through lipid metabolism. Cell Rep. 22, 3507–3520. [PubMed: 29590619]

Garcia-Barros M, et al., 2016 Role of neutral ceramidase in colon cancer. FASEB J. 30, 4159–4171. [PubMed: 27609772]

Gatenby RA, Gillies RJ, 2004 Why do cancers have high aerobic glycolysis? Nat. Rev. Cancer 4, 891–899. [PubMed: 15516961]

Gebbia V, et al., 1997 Cisplatin and epirubicin plus oral lonidamine as first-line treatment for metastatic breast cancer: a phase II study of the Southern Italy oncology group (GOIM). Anticancer Drugs 8, 943–948. [PubMed: 9436637]

Geffken K, Spiegel S, 2018 Sphingosine kinase 1 in breast cancer. Adv. Biol. Regul 67, 59–65. [PubMed: 29055687]

Giardiello FM, et al., 2002 Primary chemoprevention of familial adenomatous polyposis with sulindac. N. Engl. J. Med 346, 1054–1059. [PubMed: 11932472]

Goldberg MS, Sharp PA, 2012 Pyruvate kinase M2-specific siRNA induces apoptosis and tumor regression. J. Exp. Med 209, 217–224. [PubMed: 22271574]

Golijanin D, et al., 2004 Cyclooxygenase-2 and microsomal prostaglandin E synthase-1 are overexpressed in squamous cell carcinoma of the penis. Clin. Cancer Res 10, 1024–1031. [PubMed: 14871981]

Goncalves MD, et al., 2019 High-fructose corn syrup enhances intestinal tumor growth in mice. Science 363, 1345–1349. [PubMed: 30898933]

Gong L, et al., 2014 3-Bromopyruvic acid, a hexokinase II inhibitor, is an effective antitumor agent on the hepatoma cells: in vitro and in vivo findings. Anticancer Agents Med. Chem 14, 771–776. [PubMed: 24738957]

Goodwin J, et al., 2017 The distinct metabolic phenotype of lung squamous cell carcinoma defines selective vulnerability to glycolytic inhibition. Nat. Commun 8, 15503. [PubMed: 28548087]

Grobholz R, et al., 1993 Reduction in the expression of glucose transporter protein GLUT 2 in preneoplastic and neoplastic hepatic lesions and reexpression of GLUT 1 in late stages of hepatocarcinogenesis. Cancer Res. 53, 4204–4211. [PubMed: 8364915]

Guha M, et al., 2018 Aggressive triple negative breast cancers have unique molecular signature on the basis of mitochondrial genetic and functional defects. Biochim. Biophys. Acta Mol. basis Dis 1864, 1060–1071. [PubMed: 29309924]

Gustafsson R, et al., 2017 Crystal structure of the emerging cancer target MTHFD2 in complex with a substrate-based inhibitor. Cancer Res. 77, 937–948. [PubMed: 27899380]

Gutierrez JA, et al., 2006 An inhibitor of human asparagine synthetase suppresses proliferation of an L-asparaginase-resistant leukemia cell line. Chem. Biol 13, 1339–1347. [PubMed: 17185229]

Halter F, et al., 2001 Cyclooxygenase 2-implications on maintenance of gastric mucosal integrity and ulcer healing: controversial issues and perspectives. Gut 49, 443–453. [PubMed: 11511570]

Hanahan D, Weinberg RA, 2011 Hallmarks of cancer: the next generation. Cell 144, 646–674. [PubMed: 21376230]

Hannun YA, Obeid LM, 2008 Principles of bioactive lipid signalling: lessons from sphingolipids. Nat. Rev. Mol. Cell Biol 9, 139–150. [PubMed: 18216770]

Hannun YA, Obeid LM, 2018 Sphingolipids and their metabolism in physiology and disease. Nat. Rev. Mol. Cell Biol 19, 175–191. [PubMed: 29165427]

Hay N, 2016 Reprogramming glucose metabolism in cancer: can it be exploited for cancer therapy? Nat. Rev. Cancer 16, 635–649. [PubMed: 27634447]

He J, et al., 2014 Overexpression of microRNA-122 re-sensitizes 5-FU-resistant colon cancer cells to 5-FU through the inhibition of PKM2 in vitro and in vivo. Cell Biochem. Biophys 70, 1343–1350. [PubMed: 24898807]

He Y, et al., 2015 Pyruvate kinase isoform M2 (PKM2) participates in multiple myeloma cell proliferation, adhesion and chemoresistance. Leuk. Res 39, 1428–1436. [PubMed: 26453405]

He X, et al., 2016 Overexpression of hexokinase 1 as a poor prognosticator in human colorectal cancer. Tumour Biol. 37, 3887–3895. [PubMed: 26476538]

Hernlund E, et al., 2008 Potentiation of chemotherapeutic drugs by energy metabolism inhibitors 2-deoxyglucose and etomoxir. Int. J. Cancer 123, 476–483. [PubMed: 18452174]

Hirayama A, et al., 2009 Quantitative metabolome profiling of colon and stomach cancer microenvironment by capillary electrophoresis time-of-flight mass spectrometry. Cancer Res. 69, 4918–4925. [PubMed: 19458066]

Hochberg Z, 2018 An evolutionary perspective on the obesity epidemic. Trends Endocrinol. Metab 29, 819–826. [PubMed: 30243773]

Hopkins BD, et al., 2018 Suppression of insulin feedback enhances the efficacy of PI3K inhibitors. Nature 560, 499–503. [PubMed: 30051890]

Howe LR, et al., 2013 Genetic deletion of microsomal prostaglandin E synthase-1 suppresses mouse mammary tumor growth and angiogenesis. Prostaglandins Other Lipid Mediat. 106, 99–105. [PubMed: 23624019]

Huang Q, et al., 2011 Caspase 3-mediated stimulation of tumor cell repopulation during cancer radiotherapy. Nat. Med 17, 860–866. [PubMed: 21725296]

Huang X, et al., 2015 HK2 is a radiation resistant and independent negative prognostic factor for patients with locally advanced cervical squamous cell carcinoma. Int. J. Clin. Exp. Pathol 8, 4054–4063. [PubMed: 26097593]

Hughes D, et al., 2008 NAD+-dependent 15-hydroxyprostaglandin dehydrogenase regulates levels of bioactive lipids in non-small cell lung cancer. Cancer Prev. Res. (Phila.) 1, 241–249. [PubMed: 19138967]

Ignatenko NA, et al., 2008 Combination chemoprevention of intestinal carcinogenesis in a murine model of familial adenomatous polyposis. Nutr. Cancer 60 (Suppl. 1), 30–35. [PubMed: 19003578]

Iqbal MA, Bamezai RN, 2012 Resveratrol inhibits cancer cell metabolism by down regulating pyruvate kinase M2 via inhibition of mammalian target of rapamycin. PLoS One 7, e36764. [PubMed: 22574221]

Israelsen WJ, et al., 2013 PKM2 isoform-specific deletion reveals a differential requirement for pyruvate kinase in tumor cells. Cell 155, 397–409. [PubMed: 24120138]

Jacoby RF, et al., 2000 The cyclooxygenase-2 inhibitor celecoxib is a potent preventive and therapeutic agent in the min mouse model of adenomatous polyposis. Cancer Res. 60, 5040–5044. [PubMed: 11016626]

Jewell JL, et al., 2013 Amino acid signalling upstream of mTOR. Nat. Rev. Mol. Cell Biol 14, 133–139. [PubMed: 23361334]

Jiang K, et al., 2012 Cyclosporine A inhibits breast cancer cell growth by downregulating the expression of pyruvate kinase subtype M2. Int. J. Mol. Med 30, 302–308. [PubMed: 22580449]

Jiwa LS, et al., 2014 Upregulation of Claudin-4, CAIX and GLUT-1 in distant breast cancer metastases. BMC Cancer 14, 864. [PubMed: 25417118]

Jones SF, Infante JR, 2015 Molecular pathways: fatty acid synthase. Clin. Cancer Res 21, 5434–5438. [PubMed: 26519059]

Ju HQ, et al., 2018 Modulation of redox homeostasis by inhibition of MTHFD2 in colorectal cancer: mechanisms and therapeutic implications. J. Natl. Cancer Inst 111, 584–596.

Kapitonov D, et al., 2009 Targeting sphingosine kinase 1 inhibits Akt signaling, induces apoptosis, and suppresses growth of human glioblastoma cells and xenografts. Cancer Res. 69, 6915–6923. [PubMed: 19723667]

Kerr J, et al., 2017 Physical activity, sedentary behaviour, diet, and cancer: an update and emerging new evidence. Lancet Oncol. 18, e457–e471. [PubMed: 28759385]

Kidd EA, Grigsby PW, 2008 Intratumoral metabolic heterogeneity of cervical cancer. Clin. Cancer Res 14, 5236–5241. [PubMed: 18698042]

Kim DH, et al., 2015 Prognostic significance of intratumoral metabolic heterogeneity on 18F-FDG PET/CT in pathological N0 non-small cell lung cancer. Clin. Nucl. Med 40, 708–714. [PubMed: 26098287]

Koh YW, et al., 2017 Differential expression and prognostic significance of GLUT1 according to histologic type of non-small-cell lung cancer and its association with volume-dependent parameters. Lung Cancer 104, 31–37. [PubMed: 28212997]

Kohno M, et al., 2006 Intracellular role for sphingosine kinase 1 in intestinal adenoma cell proliferation. Mol. Cell. Biol 26, 7211–7223. [PubMed: 16980623]

Koppenol WH, et al., 2011 Otto Warburg's contributions to current concepts of cancer metabolism. Nat. Rev. Cancer 11, 325–337. [PubMed: 21508971]

Kroemer G, et al., 2018 Carbotoxicity-noxious effects of carbohydrates. Cell 175, 605–614. [PubMed: 30340032]

Kurahara H, et al., 2018 Significance of glucose transporter type 1 (GLUT-1) expression in the therapeutic strategy for pancreatic ductal adenocarcinoma. Ann. Surg. Oncol 25, 1432–1439. [PubMed: 29404819]

Kwon OH, et al., 2012 Pyruvate kinase M2 promotes the growth of gastric cancer cells via regulation of Bcl-xL expression at transcriptional level. Biochem. Biophys. Res. Commun 423, 38–44. [PubMed: 22627140]

Labuschagne CF, et al., 2014 Serine, but not glycine, supports one-carbon metabolism and proliferation of cancer cells. Cell Rep. 7, 1248–1258. [PubMed: 24813884]

Lehuede C, et al., 2016 Metabolic plasticity as a determinant of tumor growth and metastasis. Cancer Res. 76, 5201–5208. [PubMed: 27587539]

Lévesque S, et al., 2019 Trial watch: dietary interventions for cancer therapy. OncoImmunology 8, 1591878. [PubMed: 31143510]

Li Z, Zhang H, 2016 Reprogramming of glucose, fatty acid and amino acid metabolism for cancer progression. Cell. Mol. Life Sci 73, 377–392. [PubMed: 26499846]

Li W, et al., 2014 PKM2 inhibitor shikonin suppresses TPA-induced mitochondrial malfunction and proliferation of skin epidermal JB6 cells. Mol. Carcinog 53, 403–412. [PubMed: 23255458]

Li CX, et al., 2016a Prognostic value of GLUT-1 expression in oral squamous cell carcinoma: a prisma-compliant meta-analysis. Medicine (Baltimore) 95, e5324. [PubMed: 27828852]

Li W, et al., 2016b Resveratrol inhibits hexokinases II mediated glycolysis in non-small cell lung cancer via targeting Akt signaling pathway. Exp. Cell Res 349, 320–327. [PubMed: 27829129]

Li M, et al., 2017a STAT3 regulates glycolysis via targeting hexokinase 2 in hepatocellular carcinoma cells. Oncotarget 8, 24777–24784. [PubMed: 28445971]

Li W, et al., 2017b Benserazide, a dopadecarboxylase inhibitor, suppresses tumor growth by targeting hexokinase 2. J. Exp. Clin. Cancer Res 36, 58. [PubMed: 28427443]

Li L, et al., 2019 Discovery and development of small molecule modulators targeting glutamine metabolism. Eur. J. Med. Chem 163, 215–242. [PubMed: 30522056]

Liao X, et al., 2012 Aspirin use, tumor PIK3CA mutation, and colorectal-cancer survival. N. Engl. J. Med 367, 1596–1606. [PubMed: 23094721]

Lim JY, et al., 2012 Overexpression of the M2 isoform of pyruvate kinase is an adverse prognostic factor for signet ring cell gastric cancer. World J. Gastroenterol 18, 4037–4043. [PubMed: 22912555]

Lisowska B, et al., 2018 Positives and negatives of nonsteroidal anti-inflammatory drugs in bone healing: the effects of these drugs on bone repair. Drug Des. Devel. Ther 12, 1809–1814.

Liu Y, et al., 2012 A small-molecule inhibitor of glucose transporter 1 downregulates glycolysis, induces cell-cycle arrest, and inhibits cancer cell growth in vitro and in vivo. Mol. Cancer Ther 11, 1672–1682. [PubMed: 22689530]

Liu WR, et al., 2015 PKM2 promotes metastasis by recruiting myeloid-derived suppressor cells and indicates poor prognosis for hepatocellular carcinoma. Oncotarget 6, 846–861. [PubMed: 25514599]

Locasale JW, 2013 Serine, glycine and one-carbon units: cancer metabolism in full circle. Nat. Rev. Cancer 13, 572–583. [PubMed: 23822983]

Locasale JW, et al., 2011 Phosphoglycerate dehydrogenase diverts glycolytic flux and contributes to oncogenesis. Nat. Genet 43, 869–874. [PubMed: 21804546]

Loew A, et al., 2019 A role for lipid mediators in acute myeloid leukemia. Int. J. Mol. Sci 20, E2425. [PubMed: 31100828]

Logan J, Bourassa MW, 2018 The rationale for a role for diet and nutrition in the prevention and treatment of cancer. Eur. J. Cancer Prev 27, 406–410. [PubMed: 29461280]

Long QQ, et al., 2014 Fatty acid synthase (FASN) levels in serum of colorectal cancer patients: correlation with clinical outcomes. Tumour Biol. 35, 3855–3859. [PubMed: 24430360]

Ludwig DS, et al., 2018 Dietary carbohydrates: role of quality and quantity in chronic disease. BMJ 361, k2340. [PubMed: 29898880]

Ma EH, et al., 2017 Serine is an essential metabolite for effector T cell expansion. Cell Metab. 25, 345–357. [PubMed: 28111214]

Maddocks OD, et al., 2013 Serine starvation induces stress and p53-dependent metabolic remodelling in cancer cells. Nature 493, 542–546. [PubMed: 23242140]

Maddocks ODK, et al., 2017 Modulating the therapeutic response of tumours to dietary serine and glycine starvation. Nature 544, 372–376. [PubMed: 28425994]

Mahdy AE, et al., 2009 Acid ceramidase upregulation in prostate cancer cells confers resistance to radiation: AC inhibition, a potential radiosensitizer. Mol. Ther 17, 430–438. [PubMed: 19107118]

Maningat PD, et al., 2009 Gene expression in the human mammary epithelium during lactation: the milk fat globule transcriptome. Physiol. Genomics 37, 12–22. [PubMed: 19018045]

Marriott BP, et al., 2009 National estimates of dietary fructose intake increased from 1977 to 2004 in the United States. J. Nutr 139, 1228s–1235s. [PubMed: 19403716]

Martinez-Outschoorn UE, et al., 2017 Cancer metabolism: a therapeutic perspective. Nat. Rev. Clin. Oncol 14, 11–31. [PubMed: 27141887]

Mattaini KR, et al., 2016 The importance of serine metabolism in cancer. J. Cell Biol 214, 249–257. [PubMed: 27458133]

Mazurek S, et al., 2005 Pyruvate kinase type M2 and its role in tumor growth and spreading. Semin. Cancer Biol 15, 300–308. [PubMed: 15908230]

McVerry BJ, Garcia JG, 2005 In vitro and in vivo modulation of vascular barrier integrity by sphingosine 1-phosphate: mechanistic insights. Cell. Signal 17, 131–139. [PubMed: 15494205]

Mehrotra S, et al., 2006 Microsomal prostaglandin E2 synthase-1 in breast cancer: a potential target for therapy. J. Pathol 208, 356–363. [PubMed: 16353170]

Menendez JA, Lupu R, 2017 Fatty acid synthase (FASN) as a therapeutic target in breast cancer. Expert Opin. Ther. Targets 21, 1001–1016. [PubMed: 28922023]

Michaud M, et al., 2011 Autophagy-dependent anticancer immune responses induced by chemotherapeutic agents in mice. Science 334, 1573–1577. [PubMed: 22174255]

Michels J, et al., 2013 Cisplatin resistance associated with PARP hyperactivation. Cancer Res. 73, 2271–2280. [PubMed: 23554447]

Min JW, et al., 2013 INPP4B-mediated tumor resistance is associated with modulation of glucose metabolism via hexokinase 2 regulation in laryngeal cancer cells. Biochem. Biophys. Res. Commun 440, 137–142. [PubMed: 24051093]

Montrose DC, et al., 2013 S1P(1) localizes to the colonic vasculature in ulcerative colitis and maintains blood vessel integrity. J. Lipid Res 54, 843–851. [PubMed: 23296878]

Montrose DC, et al., 2016 Celecoxib alters the intestinal microbiota and metabolome in association with reducing polyp burden. Cancer Prev. Res. (Phila.) 9, 721–731. [PubMed: 27432344]

Morselli E, et al., 2010 The life span-prolonging effect of sirtuin-1 is mediated by autophagy. Autophagy 6, 186–188. [PubMed: 20023410]

Mullarky E, et al., 2016 Identification of a small molecule inhibitor of 3-phosphoglycerate dehydrogenase to target serine biosynthesis in cancers. Proc. Natl. Acad. Sci. U.S.A 113, 1778–1783. [PubMed: 26831078]

Nakanishi M, et al., 2008 Genetic deletion of mPGES-1 suppresses intestinal tumorigenesis. Cancer Res. 68, 3251–3259. [PubMed: 18451151]

Ndaru E, et al., 2019 Novel alanine serine cysteine transporter 2 (ASCT2) inhibitors based on sulfonamide and sulfonic acid ester scaffolds. J. Gen. Physiol 151, 357–368. [PubMed: 30718375]

Ngo B, et al., 2019 Targeting cancer vulnerabilities with high-dose vitamin C. Nat. Rev. Cancer 19, 271–282. [PubMed: 30967651]

Nguyen T, Le A, 2018 The metabolism of renal cell carcinomas and liver cancer. Adv. Exp. Med. Biol 1063, 107–118. [PubMed: 29946779]

Obrist F, et al., 2018 Metabolic vulnerability of cisplatin-resistant cancers. EMBO J. 37 (14), e98597. [PubMed: 29875130]

Ogretmen B, 2018 Sphingolipid metabolism in cancer signalling and therapy. Nat. Rev. Cancer 18, 33–50. [PubMed: 29147025]

Ojelabi OA, et al., 2016 WZB117 (2-fluoro-6-(m-hydroxybenzoyloxy) phenyl m-hydroxybenzoate) inhibits GLUT1-mediated sugar transport by binding reversibly at the exofacial sugar binding site. J. Biol. Chem 291, 26762–26772. [PubMed: 27836974]

Oudard S, et al., 2003 Phase II study of lonidamine and diazepam in the treatment of recurrent glioblastoma multiforme. J. Neuro-Oncol 63, 81–86.

Pacold ME, et al., 2016 A PHGDH inhibitor reveals coordination of serine synthesis and one-carbon unit fate. Nat. Chem. Biol 12, 452–458. [PubMed: 27110680]

Pahk K, et al., 2018 Metabolic tumor heterogeneity analysis by F-18 FDG PET/CT predicts mediastinal lymph node metastasis in non-small cell lung cancer patients with clinically suspected N2. Eur. J. Radiol 106, 145–149. [PubMed: 30150037]

Palmieri D, et al., 2009 Analyses of resected human brain metastases of breast cancer reveal the association between up-regulation of hexokinase 2 and poor prognosis. Mol. Cancer Res 7, 1438–1445. [PubMed: 19723875]

Papaldo P, et al., 2003 Addition of either lonidamine or granulocyte colony-stimulating factor does not improve survival in early breast cancer patients treated with high-dose epirubicin and cyclophosphamide. J. Clin. Oncol 21, 3462–3468. [PubMed: 12972521]

Pappu R, et al., 2007 Promotion of lymphocyte egress into blood and lymph by distinct sources of sphingosine-1-phosphate. Science 316, 295–298. [PubMed: 17363629]

Park YK, Yetley EA, 1993 Intakes and food sources of fructose in the United States. Am. J. Clin. Nutr 58, 737S–747S. [PubMed: 8213605]

Pchejetski D, et al., 2011 Therapeutic potential of targeting sphingosine kinase 1 in prostate cancer. Nat. Rev. Urol 8, 569–678. [PubMed: 21912422]

Perl A, et al., 2011 Oxidative stress, inflammation and carcinogenesis are controlled through the pentose phosphate pathway by transaldolase. Trends Mol. Med 17, 395–403. [PubMed: 21376665]

Pieters R, et al., 2011 L-asparaginase treatment in acute lymphoblastic leukemia: a focus on Erwinia asparaginase. Cancer 117, 238–249. [PubMed: 20824725]

Pike LS, et al., 2011 Inhibition of fatty acid oxidation by etomoxir impairs NADPH production and increases reactive oxygen species resulting in ATP depletion and cell death in human glioblastoma cells. Biochim. Biophys. Acta 1807, 726–734. [PubMed: 21692241]

Pizer ES, et al., 1997 Expression of fatty acid synthase is closely linked to proliferation and stromal decidualization in cycling endometrium. Int. J. Gynecol. Pathol 16, 45–51. [PubMed: 8986532]

Portalone L, et al., 1999 Treatment of inoperable non-small cell lung carcinoma stage IIIb and IV with cisplatin, epidoxorubicin, vindesine and lonidamine: a phase II study. Tumori 85, 239–242. [PubMed: 10587024]

Possemato R, et al., 2011 Functional genomics reveal that the serine synthesis pathway is essential in breast cancer. Nature 476, 346–350. [PubMed: 21760589]

Pudova EA, et al., 2018 HK3 overexpression associated with epithelial-mesenchymal transition in colorectal cancer. BMC Genomics 19, 113. [PubMed: 29504907]

Quinones A, Le A, 2018 The multifaceted metabolism of glioblastoma. Adv. Exp. Med. Biol 1063, 59–72. [PubMed: 29946775]

Raez LE, et al., 2013 A phase I dose-escalation trial of 2-deoxy-D-glucose alone or combined with docetaxel in patients with advanced solid tumors. Cancer Chemother. Pharmacol 71, 523–530. [PubMed: 23228990]

Ramu A, et al., 1984 Reversal of acquired resistance to doxorubicin in P388 murine leukemia cells by perhexiline maleate. Cancer Res. 44, 144–148. [PubMed: 6690032]

Ravagnan L, et al., 1999 Lonidamine triggers apoptosis via a direct, Bcl-2-inhibited effect on the mitochondrial permeability transition pore. Oncogene 18, 2537–2546. [PubMed: 10353597]

Rivera J, et al., 2008 The alliance of sphingosine-1-phosphate and its receptors in immunity. Nat. Rev. Immunol 8, 753–763. [PubMed: 18787560]

Rodic S, Vincent MD, 2018 Reactive oxygen species (ROS) are a key determinant of cancer's metabolic phenotype. Int. J. Cancer 142, 440–448. [PubMed: 28940517]

Rodrigues M, et al., 2019 Wound healing: a cellular perspective. Physiol. Rev 99, 665–706. [PubMed: 30475656]

Rybstein MD, et al., 2018 The autophagic network and cancer. Nat. Cell Biol 20, 243–251. [PubMed: 29476153]

Saavedra-Garcia P, et al., 2018 Unravelling the role of fatty acid metabolism in cancer through the FOXO3-FOXM1 axis. Mol. Cell. Endocrinol 462, 82–92. [PubMed: 28087388]

Samudio I, et al., 2010 Pharmacologic inhibition of fatty acid oxidation sensitizes human leukemia cells to apoptosis induction. J. Clin. Invest 120, 142–156. [PubMed: 20038799]

Sandborn WJ, et al., 2016 Ozanimod induction and maintenance treatment for ulcerative colitis. N. Engl. J. Med 374, 1754–1762. [PubMed: 27144850]

Sasaki Y, et al., 2012 Microsomal prostaglandin E synthase-1 is involved in multiple steps of colon carcinogenesis. Oncogene 31, 2943–2952. [PubMed: 21986945]

Schcolnik-Cabrera A, et al., 2018 Orlistat as a FASN inhibitor and multitargeted agent for cancer therapy. Expert Opin. Investig. Drugs 27, 475–489.

Schmelz EM, et al., 1996 Sphingomyelin consumption suppresses aberrant colonic crypt foci and increases the proportion of adenomas versus adenocarcinomas in CF1 mice treated with 1,2-

dimethylhydrazine: implications for dietary sphingolipids and colon carcinogenesis. Cancer Res. 56, 4936–4941. [PubMed: 8895747]

Schooneman MG, et al., 2013 Acylcarnitines: reflecting or inflicting insulin resistance? Diabetes 62, 1–8. [PubMed: 23258903]

Schulte ML, et al., 2018 Pharmacological blockade of ASCT2-dependent glutamine transport leads to antitumor efficacy in preclinical models. Nat. Med 24, 194–202. [PubMed: 29334372]

Seelan RS, et al., 2000 Human acid ceramidase is overexpressed but not mutated in prostate cancer. Genes Chromosom. Cancer 29, 137–146. [PubMed: 10959093]

Selzner M, et al., 2001 Induction of apoptotic cell death and prevention of tumor growth by ceramide analogues in metastatic human colon cancer. Cancer Res. 61, 1233–1240. [PubMed: 11221856]

Shimizu Y, et al., 2018 Genetic deletion of sphingosine kinase 1 suppresses mouse breast tumor development in an HER2 transgenic model. Carcinogenesis 39, 47–55. [PubMed: 28968647]

Sica V, et al., 2015 Organelle-specific initiation of autophagy. Mol. Cell 59, 522–539. [PubMed: 26295960]

Siebeneicher H, et al., 2016 Identification and optimization of the first highly selective GLUT1 inhibitor BAY-876. ChemMedChem 11, 2261–2271. [PubMed: 27552707]

Sigthorsson G, et al., 2002 COX-1 and 2, intestinal integrity, and pathogenesis of nonsteroidal anti-inflammatory drug enteropathy in mice. Gastroenterology 122, 1913–1923. [PubMed: 12055598]

Silverstein FE, et al., 2000 Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. Celecoxib long-term arthritis safety study. JAMA 284, 1247–1255. [PubMed: 10979111]

Simmons DL, et al., 2004 Cyclooxygenase isozymes: the biology of prostaglandin synthesis and inhibition. Pharmacol. Rev 56, 387–437. [PubMed: 15317910]

Singh D, et al., 2005 Optimizing cancer radiotherapy with 2-deoxy-d-glucose dose escalation studies in patients with glioblastoma multiforme. Strahlenther. Onkol 181, 507–514. [PubMed: 16044218]

Slominski AT, et al., 2018 Melatonin: a cutaneous perspective on its production, metabolism, and functions. J. Invest. Dermatol 138, 490–499. [PubMed: 29428440]

Song M, et al., 2018 Recent development of small molecule glutaminase inhibitors. Curr. Top. Med. Chem 18, 432–443. [PubMed: 29793408]

Steinbach G, et al., 2000 The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. N. Engl. J. Med 342, 1946–1952. [PubMed: 10874062]

Suh DH, et al., 2014a Association of overexpression of hexokinase II with chemoresistance in epithelial ovarian cancer. Clin. Exp. Med 14, 345–353. [PubMed: 23949336]

Suh DH, et al., 2014b Metabolic orchestration between cancer cells and tumor microenvironment as a co-evolutionary source of chemoresistance in ovarian cancer: a therapeutic implication. Biochem. Pharmacol 92, 43–54. [PubMed: 25168677]

Sun H, et al., 2015 Knockdown of PKM2 suppresses tumor growth and invasion in lung adenocarcinoma. Int. J. Mol. Sci 16, 24574–24587. [PubMed: 26501265]

Susin SA, et al., 1997 The central executioner of apoptosis: multiple connections between protease activation and mitochondria in Fas/APO-1/CD95- and ceramide-induced apoptosis. J. Exp. Med 186, 25–37. [PubMed: 9206994]

Sutow WW, et al., 1971 L-asparaginase therapy in children with advanced leukemia. The Southwest Cancer Chemotherapy Study Group. Cancer 28, 819–824. [PubMed: 5286444]

Tait SW, Green DR, 2010 Mitochondria and cell death: outer membrane permeabilization and beyond. Nat. Rev. Mol. Cell Biol 11, 621–632. [PubMed: 20683470]

Tamada M, et al., 2012 Pyruvate kinase M2: multiple faces for conferring benefits on cancer cells. Clin. Cancer Res 18, 5554–5561. [PubMed: 23071357]

Tan SF, et al., 2016 Acid ceramidase is upregulated in AML and represents a novel therapeutic target. Oncotarget 7, 83208–83222. [PubMed: 27825124]

Tennant DA, et al., 2010 Targeting metabolic transformation for cancer therapy. Nat. Rev. Cancer 10, 267–277. [PubMed: 20300106]

Thamrongwaranggoon U, et al., 2017 Targeting hexokinase II as a possible therapy for cholangiocarcinoma. Biochem. Biophys. Res. Commun 484, 409–415. [PubMed: 28131825]

Thiefin G, Beaugerie L, 2005 Toxic effects of nonsteroidal antiinflammatory drugs on the small bowel, colon, and rectum. Joint Bone Spine 72, 286–294. [PubMed: 16038840]

Thupari JN, et al., 2001 Fatty acid synthase inhibition in human breast cancer cells leads to malonyl-CoA-induced inhibition of fatty acid oxidation and cytotoxicity. Biochem. Biophys. Res. Commun 285, 217–223. [PubMed: 11444828]

Tirado-Velez JM, et al., 2012 Inhibition of fatty acid metabolism reduces human myeloma cells proliferation. PLoS One 7, e46484. [PubMed: 23029529]

Vander Heiden MG, 2011 Targeting cancer metabolism: a therapeutic window opens. Nat. Rev. Drug Discov 10, 671–684. [PubMed: 21878982]

Vander Linden C, Corbet C, 2019 Reconciling environment-mediated metabolic heterogeneity with the oncogene-driven cancer paradigm in precision oncology. Semin. Cell Dev. Biol

Vella S, et al., 2015 Perhexiline maleate enhances antitumor efficacy of cisplatin in neuroblastoma by inducing over-expression of NDM29 ncRNA. Sci. Rep 5, 18144. [PubMed: 26674674]

Vie N, et al., 2008 Overexpression of phosphoserine aminotransferase PSAT1 stimulates cell growth and increases chemoresistance of colon cancer cells. Mol. Cancer 7, 14. [PubMed: 18221502]

Vijayan Y, et al., 2019 Acid ceramidase; A novel therapeutic target in cancer. Curr. Top. Med. Chem

Vitale I, et al., 2019 Mutational and antigenic landscape in tumor progression and cancer immunotherapy. Trends Cell Biol. 29, 396–416. [PubMed: 30765144]

Wallace JL, Devchand PR, 2005 Emerging roles for cyclooxygenase-2 in gastrointestinal mucosal defense. Br. J. Pharmacol 145, 275–282. [PubMed: 15778736]

Walter K, et al., 2009 Serum fatty acid synthase as a marker of pancreatic neoplasia. Cancer Epidemiol. Biomark. Prev 18, 2380–2385.

Wang L, Dudek SM, 2009 Regulation of vascular permeability by sphingosine 1-phosphate. Microvasc. Res 77, 39–45. [PubMed: 18973762]

Wang Y, et al., 2015a Overexpression of pyruvate kinase M2 associates with aggressive clinicopathological features and unfavorable prognosis in oral squamous cell carcinoma. Cancer Biol. Ther 16, 839–845. [PubMed: 25970228]

Wang BY, et al., 2015b Intermittent high dose proton pump inhibitor enhances the antitumor effects of chemotherapy in metastatic breast cancer. J. Exp. Clin. Cancer Res 34, 85. [PubMed: 26297142]

Wang H, et al., 2016 Inhibition of glycolytic enzyme hexokinase II (HK2) suppresses lung tumor growth. Cancer Cell Int. 16, 9. [PubMed: 26884725]

Wang Q, et al., 2017 Rational design of selective allosteric inhibitors of PHGDH and serine synthesis with anti-tumor activity. Cell Chem. Biol 24, 55–65. [PubMed: 28042046]

Wang Y, et al., 2018 Eicosanoid signaling in carcinogenesis of colorectal cancer. Cancer Metastasis Rev. 37, 257–267. [PubMed: 29858741]

Warburg O, 1924 Uberden Stoffwechsel der Carcinomzelle. Biochem. Z 152, 309–344.

Whittle BJ, 2004 Mechanisms underlying intestinal injury induced by anti-inflammatory COX inhibitors. Eur. J. Pharmacol 500, 427–439. [PubMed: 15464050]

Wise DR, Thompson CB, 2010 Glutamine addiction: a new therapeutic target in cancer. Trends Biochem. Sci 35, 427–433. [PubMed: 20570523]

Witkiewicz AK, et al., 2008 Co-expression of fatty acid synthase and caveolin-1 in pancreatic ductal adenocarcinoma: implications for tumor progression and clinical outcome. Cell Cycle 7, 3021–3025. [PubMed: 18802406]

Wolf I, et al., 2006 15-hydroxyprostaglandin dehydrogenase is a tumor suppressor of human breast cancer. Cancer Res. 66, 7818–7823. [PubMed: 16885386]

Wu J, et al., 2017 Poor prognosis of hexokinase 2 overexpression in solid tumors of digestive system: a meta-analysis. Oncotarget 8, 32332–32344. [PubMed: 28415659]

Yan M, et al., 2004 15-Hydroxyprostaglandin dehydrogenase, a COX-2 oncogene antagonist, is a TGF-beta-induced suppressor of human gastrointestinal cancers. Proc. Natl. Acad. Sci. U.S.A 101, 17468–17473. [PubMed: 15574495]

Yang M, Vousden KH, 2016 Serine and one-carbon metabolism in cancer. Nat. Rev. Cancer 16, 650–662. [PubMed: 27634448]

Yang M, et al., 2013 Oncometabolites: linking altered metabolism with cancer. J. Clin. Invest 123, 3652–3658. [PubMed: 23999438]

Ye J, et al., 2018 Targeting of glutamine transporter ASCT2 and glutamine synthetase suppresses gastric cancer cell growth. J. Cancer Res. Clin. Oncol 144, 821–833. [PubMed: 29435734]

Yin J, et al., 2018 Protein restriction and cancer. Biochim. Biophys. Acta Rev. Cancer 1869, 256–262. [PubMed: 29596961]

Yoo JJ, et al., 2019 Hexokinase-II inhibition synergistically augments the anti-tumor efficacy of sorafenib in hepatocellular carcinoma. Int. J. Mol. Sci 20 (6), E1292. [PubMed: 30875800]

Yoshida GJ, 2015 Metabolic reprogramming: the emerging concept and associated therapeutic strategies. J. Exp. Clin. Cancer Res 34, 111. [PubMed: 26445347]

Yoshimatsu K, et al., 2001a Inducible prostaglandin E synthase is overexpressed in non-small cell lung cancer. Clin. Cancer Res 7, 2669–2674. [PubMed: 11555578]

Yoshimatsu K, et al., 2001b Inducible microsomal prostaglandin E synthase is overexpressed in colorectal adenomas and cancer. Clin. Cancer Res 7, 3971–3976. [PubMed: 11751489]

Yu Q, et al., 2016 Knockdown of asparagine synthetase (ASNS) suppresses cell proliferation and inhibits tumor growth in gastric cancer cells. Scand. J. Gastroenterol 51, 1220–1226. [PubMed: 27251594]

Yuan C, et al., 2014 Overexpression of metabolic markers PKM2 and LDH5 correlates with aggressive clinicopathological features and adverse patient prognosis in tongue cancer. Histopathology 65, 595–605. [PubMed: 24762230]

Zadra G, et al., 2019 Inhibition of de novo lipogenesis targets androgen receptor signaling in castration-resistant prostate cancer. Proc. Natl. Acad. Sci. U.S.A 116, 631–640. [PubMed: 30578319]

Zhan C, et al., 2013 Pyruvate kinase M2 is highly correlated with the differentiation and the prognosis of esophageal squamous cell cancer. Dis. Esophagus 26, 746–753. [PubMed: 23317289]

Zhang Q, et al., 2014a Hexokinase II inhibitor, 3-BrPA induced autophagy by stimulating ROS formation in human breast cancer cells. Genes Cancer 5, 100–112. [PubMed: 25053988]

Zhang Y, et al., 2014b Sphingosine kinase 1 and cancer: a systematic review and meta-analysis. PLoS One 9, e90362. [PubMed: 24587339]

Zhang B, et al., 2017 PHGDH defines a metabolic subtype in lung adenocarcinomas with poor prognosis. Cell Rep. 19, 2289–2303. [PubMed: 28614715]

Zhang XY, et al., 2018 Hexokinase 2 confers resistance to cisplatin in ovarian cancer cells by enhancing cisplatin-induced autophagy. Int. J. Biochem. Cell Biol 95, 9–16. [PubMed: 29247711]

Zhang B, et al., 2019 The clinicopathologic impacts and prognostic significance of GLUT1 expression in patients with lung cancer: a meta-analysis. Gene 689, 76–83. [PubMed: 30552981]

Zhou W, et al., 2003 Fatty acid synthase inhibition triggers apoptosis during S phase in human cancer cells. Cancer Res. 63, 7330–7337. [PubMed: 14612531]

Zhou CF, et al., 2012 Pyruvate kinase type M2 is upregulated in colorectal cancer and promotes proliferation and migration of colon cancer cells. IUBMB Life 64, 775–782. [PubMed: 22807066]

Zhou Y, et al., 2018 MiR-34a, as a suppressor, enhance the susceptibility of gastric cancer cell to luteolin by directly targeting HK1. Gene 644, 56–65. [PubMed: 29054762]

Zhu J, Thompson CB, 2019 Metabolic regulation of cell growth and proliferation. Nat. Rev. Mol. Cell Biol 20, 436–450. [PubMed: 30976106]