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Cancer cell metabolism in tumor-targeting immunity

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Abstract

Accumulating evidence suggests that metabolic rewiring in malignant cells supports tumor progression not only by providing them with a superior proliferative potential and an increased adaptability to adverse microenvironmental conditions, but also by favoring the evasion of natural and therapy driven anticancer immunosurveillance. Here, we review cancer cell-intrinsic and extrinsic mechanisms through which alterations of metabolism in malignant cells interfere with innate and adaptive immune functions in support of accelerated disease progression, and we discuss the potential of targeting such alterations to enhance anticancer immunity for therapeutic purposes.

Keywords

autophagy; fatty acid synthesis; glycolysis; immunometabolism; T cells; tumor-associated macrophages

Introduction

Malignant transformation and tumor progression are accompanied by numerous alterations in metabolic pathways that emerge in the context of at least three conceptually different (but not mutually exclusives) scenarios[1,2]. First, metabolites that accumulate because of mutations in enzyme-coding genes are the primary drivers for oncogenesis. As an example, this occurs downstream of gain-of-function isocitrate dehydrogenase (NADP(+)) 1 (*IDH1*) or *IDH2* mutations (which are common in patients with glioblastoma and leukemia), resulting in the accumulation of 2-hydroxyglutarate [2HG], which has *bona fide* tumor-promoting activity[3]. Second, genetic or epigenetic alterations in well-established

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oncoproteins or oncosuppressors drive oncogenesis along with a direct influence on metabolism. Indeed, multiple cancer-initiating events such as activating mutations in KRAS proto-oncogene, GTPase (*KRAS*) as well as the genetic or epigenetic inactivation of the tumor protein p53 (TP53, best known as TP53) have been shown to directly impact **catabolism** or **anabolism**[4,5]. Third, cancer cells acquire metabolic alterations as tumors evolve in response to spatiotemporally changing microenvironmental conditions, one of the major driver of intra- and inter-tumor heterogeneity[6]. As an example, malignant cells not located in the close proximity of blood vessels respond to hypoxia with a global metabolic reconfiguration orchestrated by hypoxia inducible factor 1 subunit alpha (HIF1A)[7]. Of note, though conceptually distinct, all these scenarios generate metabolic vulnerabilities that (at least theoretically) may be targeted for therapeutic purposes[8,9].

Initiated a century ago by the German physiologist Otto H. Warburg with the observation that malignant cells take up an increased amount of glucose as compared to their normal counterparts[10], the field of cancer metabolism has by now revealed that malignant transformation and tumor progression involve a cell-wide metabolic rewiring that goes way beyond the so-called Warburg effect[2]. Indeed, cancer cells often exhibit complex metabolic alterations that also affect **oxidative phosphorylation (OXPHOS)**, the **tricarboxylic acid (TCA) cycle**, multiple biosynthetic cascades, as well as global catabolic pathways such as autophagy[2,11]. Such changes (which often influence the tumor stroma, Box 1) provide malignant cells with the metabolic substrates that are required to enable accelerated proliferation, including (but not limited to) nucleotides, lipids and amino acids as needed for cellular growth and division[2,11]. Moreover, the metabolic rewiring that characterize most (if not all) cancer cells endow them with a superior adaptability to changing microenvironmental conditions, *de facto* fostering tumor evolution and diversification[6,12]. Accumulating data indicate that malignant cells also benefit from metabolic changes that counteract a major selective pressure in the host-tumor co-evolution, namely, anticancer immunosurveillance[13]. Indeed, it is now widely accepted that oncogenesis is not a merely cancer cell-intrinsic phenomenon driven by genetic and/or epigenetic alterations that support malignancy, but it also involves a prominent cancer cell-extrinsic component, *i.e.*, the acquisition of phenotypic, secretory and behavioral features that enable cancer cells to evade recognition and killing by the host immune system[13].

Here, we discuss mechanisms through which alterations of core metabolism in neoplastic cells influence natural and therapy-driven immunosurveillance as we analyze the potential of targeting such changes to enhance anticancer immune responses for therapeutic purposes. Importantly, macromolecular metabolic pathways including DNA replication, DNA-to-RNA transcription and protein synthesis, despite their potential impact on tumor-targeting immunity,[14,15] go beyond the scope of this review. Along similar lines, the influence of immune cell metabolism on tumor-targeting immunity has been extensively reviewed elsewhere[16–18], and hence will not be discussed here.

Glucose, lactate, and the TCA cycle

To meet their increased energy demand, cancer cells generally exhibit an accelerated and diversified bioenergetic metabolism, involving an enhanced glucose flux through glycolysis

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as well as alterations of the TCA cycle. All these metabolic changes influence tumor-targeting immunity (Fig. 1).

Glucose.

Malignant cells use glucose for bioenergetic purposes upon conversion to pyruvate, mitochondrial uptake and entry in the TCA cycle, as well as for anabolic purposes via the **pentose phosphate pathway (PPP)** and the serine synthesis pathway (SSP)[19]. Thus, cancer cells may be in competition with immune cells, notably $CD8^+$ cytotoxic T lymphocytes (CTLs), for glucose uptake in the tumor microenvironment (TME) of some malignancies, as demonstrated in immunocompetent mouse models of sarcoma[20]. However, it appears that immune cells generally consume more glucose than cancer cells themselves, and that glutamine (rather than glucose itself) is the limiting nutrient that determines differential glucose uptake by malignant vs immune compartments of the TME[21]. That said, an increased glycolytic flux in melanoma cells has been associated with limited expression of chemotactic factors involved in CTL recruitment, such as C-X-C motif chemokine ligand 10 (CXCL10)[22]. In line with this observation, genetic signatures of glycolysis have been shown to inversely correlate with immune cell infiltration in patients with melanoma and non-small cell lung carcinoma (NSCLC), in the former setting especially amongst patients refractory to adoptive T cell transfer[22]. Moreover, elevated glucose intake has been linked with the hexokinase 2 (HK2)-dependent activation of an NF-κB transcriptional response culminating with the expression of the co-inhibitory ligand CD274 (best known as PD-L1) in models of glioblastoma[23]. Finally, increase glycolytic flux has been linked with the overexpression of colony stimulating factor 1 (CSF1, best known as M-CSF) and CSF2 (best known as GM-CSF) by triple negative breast cancer (TNBC) cells, resulting in the repolarization of the TME towards an immunosuppressive state dominated by myeloid-derived suppressor cells (MDSCs)[24]. Interestingly, patients with TNBC from the METABRIC public dataset with an elevated expression of lactate dehydrogenase A (*LDHA*, encoding for the final enzyme of anerobic glycolysis, which diverts pyruvate from mitochondrial uptake to conversion into lactate and secretion) were found to exhibit an enrichment in gene signatures associated with MDSCs coupled with an underrepresentation of gene signatures representative of T cell infiltration, and exhibited poor disease outcome[24]. Most likely, however, these observations do not stem only from the immunosuppressive effects of lactate (see below), but also reflects the elevated LDHA levels found in myeloid cells including MDSCs themselves.

In line with an immunosuppressive role for glycolysis in cancer cells, several pharmacological or genetic strategies for glycolysis inhibition have been shown to mediate immunostimulatory effects and restore (at least partially) immunosurveillance in preclinical tumor models. For instance, genetic inhibition of glycolysis in mouse lung carcinoma LLC cells and mouse pancreatic cancer Panc02 cells as imposed by the deletion of solute carrier family 2 (facilitated glucose transporter), member 1 (*Slc2a1*, best known as *Glut1*), which encodes a plasma membrane glucose channel, or glucose-6-phosphate isomerase 1 (*Gpi1*), which encodes an isomerase catalyzing the interconversion of glucose-6-phosphate (G6P) and fructose-6-phosphate (F6P), in has been shown to increase the sensitivity of malignant cells to CTLs[25]. Mechanistically, such an immune sensitization originated from accelerated OXPHOS coupled with reactive oxygen species (ROS) overproduction and

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increased sensitivity to tumor necrosis factor (TNF)-driven cell death[25]. Whether *Glut1* or *Gpi1* deletion also alters antigen presentation by cancer cells remains to be investigated. Irrespective of this incognita, both *GLUT1* levels and genetic signatures of glycolysis were associated with limited T cell infiltration in patients with various tumors[25]. Moreover, in patients with lung or pancreatic adenocarcinoma, transcriptional markers of elevated glycolysis and reduced TNF signaling were linked with poor overall survival[25]. These findings exemplify the clinical relevance of suppressed anticancer immunity as driven by glycolysis in cancer cells.

In summary, glucose metabolism in cancer cells may have immunosuppressive effects on the TME. Of note, glucose-dependent immunosuppression at least partially originates from lactate secretion, potentially offering an improved target for therapeutic interventions (as discussed here below).

Lactate.

Lactate is abundant in most solid tumors, mediating not only trophic functions[26], but also eliciting multiple mechanisms of immunosuppression[27]. For instance, lactate has been shown to inhibit CTL cytotoxicity by limiting the replenishment of TCA cycle intermediates via pyruvate carboxylase (PC), resulting in the accumulation of pyruvate dehydrogenase (PDH), limited secretion of succinate and hence poor pro-inflammatory autocrine/paracrine signaling via succinate receptor 1 (SUCNR1), at least in transplantable mouse models of melanoma and colorectal carcinoma (CRC)[28]. Lactate also represses effector T cell proliferation by blocking glyceraldehyde 3-phosphate dehydrogenase (GAPDH) and phosphoglycerate dehydrogenase (PHGDH), which results in the deprivation of key post-GAPDH glycolytic intermediates and serine[29], as well as by promoting lysosomal acidification, which interferes with diacylglycerol-dependent protein kinase C theta (PRKCQ) signaling[30]. In line with this notion, LDHA-deficient mouse B16 melanomas exhibit a decreased growth rate than their wild-type counterparts when established subcutaneously in immunocompetent (but not immunodeficient *Rag2*$^{-/-}$*Il2Rg*$^{-/-}$) syngeneic hosts, an altered immunological control associated with increased tumor infiltration by interferon gamma (IFNG)-producing CTLs and natural killer (NK) cells[31]. That said, systemic inhibition of LDHA with the small molecule NCI-006 reportedly mediates anticancer effects in athymic mice bearing human pancreatic cancer MIA PaCa-2 xenografts[32]. Whether such an anticancer activity emerges from a direct effect on malignant cells or instead involves immune TME compartments other than T cells, however, remains to be formally established. Of note, high-dose daily i.p. lactate administration has been shown to control the growth of mouse I3TC mammary and MC38 colorectal cancers established subcutaneously in immunocompetent syngeneic mice[33]. Supporting a role for CD8$^+$ CTLs in these observations, the subcutaneous administration of lactate (but not glucose) reportedly elicits the CTL-dependent control of MC38 tumors evolving in immunocompetent syngeneic mice as a consequence of improved CD8$^+$ T cell stemness[34]. These latter findings suggest that the detrimental effects of lactate on anticancer immunity may at least partially stem by local acidification.

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At odds with their effector counterparts, immunosuppressive $CD4^+CD25^+FOXP3^+$ regulatory T (T_{REG}) cells are considerably resistant to the antiproliferative effects of lactate, at least in part as a direct consequence of the metabolic reprogramming imposed by forkhead box P3 (FOXP3), which involves active glycolysis suppression in favor of NADH oxidation and OXPHOS[35]. T_{REG} cells actually appear to abundantly import extracellular lactate via solute carrier family 16 member 1 (SLC16A1, best known as MCT1) resulting in increased PD-1 expression via a nuclear factor of activated T cells 1 (NFATC1)-dependent mechanism, as documented in immunocompetent models melanoma and CRC in mice[36]. In the same models as well as in transplantable models of head and neck squamous cell carcinoma (HNSCC), MCT1 expression appears indeed to be required for intratumoral (but not circulating) T_{REG} cells to preserve their immunosuppressive and tumor-promoting functions[37], at least in part reflecting the ability of intracellular lactate accumulation to promote the **lactylation** of moesin (MSN), hence favoring immunosuppressive transforming growth factor beta 1 (TGFB1) signaling via SMAD family member 3 (SMAD3)[38]. Of note, histone lactylation has also been proposed to mediate immunosuppressive and hence tumor-promoting effects in the myeloid compartment of transplantable (B16) mouse melanomas as well transplantable (MC38) and carcinogen-induced mouse CRCs[39]. The translational relevance of these observations, however, remains to be defined.

Interestingly, in mouse melanomas, hepatocellular carcinomas (HCCs) and CRCs that are naturally glycolytic or are genetically engineered to exhibit an elevated glycolysis (but not in their poorly glycolytic counterparts), programmed cell death 1 (PDCD1, best known as PD-1) blockage actively promotes the immunosuppressive activity of T_{REG} cells and hence has no therapeutic effects, a resistance phenotype that can be successfully reverted by pharmacological or genetic LDHA inhibition[36,38]. On the contrary, mouse TNBCs with reduced glycolytic activity have been shown to respond to immune checkpoint inhibitors (ICIs) specific for cytotoxic T lymphocyte-associated protein 4 (CTLA4) along with the destabilization of tumor-infiltrating T_{REG} cells and their shift toward an effector-like state characterized by the secretion of TNF and IFNG[40]. The relative contribution of extracellular lactate (*vs*. glucose) availability to these latter observations, however, remains to be clearly defined.

Of note, lactate also influences intratumoral myeloid cells. For instance, lactate appears to signal to tumor-associated macrophages (TAMs) via G protein-coupled receptor 132 (GPR132), resulting in their repolarization towards an immunosuppressive “M2-like” phenotype associated with increased metastatic dissemination in mouse models of TNBC[41]. Supporting the clinical relevant of preclinical these observations, *GPR132* levels have been shown to positively correlated with genetic signatures of M2-like TAMs as well as increased metastatic dissemination and poor disease outcome in a cohort of patients with TNBC[41]. Similar results have been obtained in preclinical models of lung carcinoma as driven by the loss of serine/threonine kinase 11 (*Stk11*), although in this latter case extracellular lactate accumulated downstream of solute carrier family 16 member 4 (SLC16A4, best known as MCT4) overexpression and appeared to signal to TAMs (and CTLs) via hydroxycarboxylic acid receptor 1 (HCAR1, also known as GPR81)[42]. While the reasons underlying such an apparent discrepancy have not yet been clarified, it is plausible that TAMs infiltrating

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different neoplasms like TNBC and lung carcinoma might express different lactate-sensitive receptors or signal transducers thereof, reflecting the well-established heterogeneity of TAMs at large[43].

Taken together, these observations suggest that at least part of the immunosuppressive effects of deregulated glucose metabolism originate from the intratumoral accumulation of lactate.

The TCA cycle.

The TCA is critical not only to provide reducing equivalent for OXPHOS but also to regulate the pool of numerous metabolites that have both metabolic and signaling functions, such as acetyl-CoA, citrate, fumarate, α-ketoglutarate (α-KG), and succinate[44,45]. Not surprisingly, many of these metabolic intermediates have also direct or indirect immunomodulatory effects. For instance, mouse B16 melanomas depleted of the TCA cycle enzyme fumarate hydratase (FH) exhibit high intratumoral levels of fumarate irrespective of potential alterations in glycolysis, resulting in acute T cell dysfunction as a consequence of the non-enzymatic succination of zeta chain of T cell receptor associated protein kinase 70 (ZAP70)[46]. In line with this notion, engineered CD19-specific CAR T cells for FH overexpression has been shown to result in superior therapeutic efficacy against human CD19-expressing leukemia cells expanding in immunocompromised mice[46]. The loss of FH also destabilizes the mitochondrial network to promote the release of small vesicles containing mitochondrial nucleic acids via a sorting nexin 9 (SNX9)-dependent mechanism, at least in preclinical models of hereditary leiomyomatosis and renal cell carcinoma (HLRCC)[47]. In this setting, the release of mitochondrial DNA (mtDNA) and mtRNA into the cytosol was shown to drive type I interferon (IFN) secretion upon activation of cyclic GMP-AMP synthase (cGAS) and RNA sensor RIG-I (RIGI)[47], a chronic, indolent inflammatory response potentially supporting oncogenesis in the context of compromised immunosurveillance[48,49].

Interestingly, a normal flow of electrons through the mitochondrial respiratory complexes that mediate OXPHOS has been recently shown to limit the recognition of melanoma cells by CTLs[50]. Such an immunosuppressive effect originates from the ability of respiratory complex II to efficiently convert succinate into fumarate, hence preventing the activation of a succinate-dependent epigenetic mechanism resulting in the upregulation of MHC class I molecules and other components of the antigen-presenting machinery[50]. These findings suggest that defects in mitochondrial electron flow that may emerge in some cancer cells during tumor evolution may be the target of negative selective pressure by the host immune system. That said, succinate accumulation in mouse TNBC cells as driven by TAM-derived TGFB1 has been shown to promote glycolysis and hence an overall immunosuppressive phenotype (see above)[51]. While the reasons for such an apparent discrepancy remain to be defined, it is plausible that tumor-specific mechanisms beyond glycolysis may underlie the immunosuppressive effects of succinate accumulation in TNBC but not melanoma cells, potentially including the succinate-dependent accumulation of hypoxia inducible factor 1 subunit alpha (HIF1A) (Box 3).

2HG also mediates *bona fide* oncogenic functions via epigenetic mechanisms, especially (but not exclusively) upon the inhibition of multiple α-KG-dependent dioxygenases, prolyl-hydroxylases and histone demethylases[3]. Moreover, the *D* enantiomer of 2HG (but not its *L* counterpart) can be actively taken up by tumor-infiltrating T lymphocytes, resulting in a dose-dependent and fully reversible inhibition of proliferation and effector functions, including IFNγ secretion, in immunocompetent mouse models of melanoma and CRC[52]. At least in part, such an immunosuppressive effect appears to originate from the ability of *D*-2HG to (1) inhibit LDHA, resulting in a metabolic shift towards OXPHOS as driven by an increased mitochondrial uptake of pyruvate and lowered NAD+/NADPH ratio[52], and (2) to disrupt nuclear factor of activated T cells 1 (NFCAT1) activity and polyamine synthesis[53].

Interestingly, another metabolic intermediate that inhibits α-KG-dependent dioxygenases, notably glutarate, has been shown to have a positive, rather than negative, influence on T cell functions[54]. Specifically, the administration of the cell permeant glutarate precursor diethyl-glutarate has been associated with improved T cell cytotoxicity against mouse B16 melanoma and SKOV3 ovarian carcinoma cells downstream of the PDH glutarylation and consequent inhibition of OXPHOS in favor of anaerobic glycolysis[54]. These findings point to glutarate metabolism as a potential target to improve T cell-dependent anticancer immune responses. Along similar lines, it has recently been shown that blocking acyl-CoA synthetase short chain family member 2 (ACSS2) – which converts acetate into acetyl-CoA – in breast cancer cells converts them from consumers to producers of acetate, resulting in abundant acetate accumulation in the TME[55]. Such microenvironmental acetate can be avidly taken up by tumor-infiltrating T lymphocytes supporting a therapeutically actionable improvement in T-cell effector functions and proliferation[55]. As these effects are observed under pharmacological ACSS2 inhibition, they are unlikely to emerge from epigenetic alterations in T cells as driven by the ACSS2-dependnent conversion of acetate into acetyl-CoA, but may instead relate to acetate signaling via free fatty acid receptor 2 (FFAR2, best known as GPR43)[56]. Of note, the TCA intermediate itaconate also appears to mediate multipronged immunosuppressive effects in a variety of cell types, including immune cell themselves[57,58]. In line with this notion, the itaconate-dependent activation of NFE2 like bZIP transcription factor 2 (NFE2L2, best known as NRF2) by a cell-permeant precursor of itaconate has been shown to suppress type I IFN responses downstream of stimulator of interferon response cGAMP interactor 1 (STING1) activation in cultured human NSCLC A549 cells[59]. To the best of our knowledge, however, the precise impact of cancer cell-derived itaconate on anticancer immune responses as emerging in immunocompetent mice bearing syngeneic tumors remain to be formally investigated.

In summary, multiple cancer-associated alterations of metabolism have been shown to elicit microenvironmental perturbations negatively affecting immunosurveillance.

Lipid metabolism

Accelerated proliferation as exhibited by transformed cells heavily relies on enhanced lipid metabolism, not only as an extra energy source downstream of fatty acid oxidation (FAO)-driven OXPHOS, but also as a source of cellular membranes and other lipid constituents

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generated by fatty acid synthesis. Cancer-associated alterations of FAO and fatty acid synthesis have been shown to impact tumor-targeting immune responses (Fig. 2)

Fatty acid oxidation.

FAO consists in the catabolism of long chain fatty acids into acetyl-CoA as a substrate for the TCA cycle to fuel OXPHOS[60]. Multiple cancer types such as glioblastoma (GBM) exhibit elevated rates of FAO in support of aggressive disease progression[61]. In this setting, the co-upregulation of multiple FAO-related enzymes such as carnitine palmitoyltransferase 1A (CPT1A), CPT2 and acyl-CoA dehydrogenase family member 9 (ACAD9) has appear to occur along with an increased exposure of CD47 on the GBM cell membrane, resulting in a potent inhibition of phagocytosis by myeloid cells and radioresistance, mechanistically reflecting the ability of FAO-derived acetyl-CoA to drive NF-κB signaling[62]. Supporting the therapeutic relevance of these observations, combining radiotherapy with a CPT1 inhibitor and a CD47 blocker was shown to result in superior tumor control in preclinical models of GBM[62]. Of note, acetyl-CoA is also a potent inhibitor of autophagy[63], which also has potent immunomodulatory activities (Box 2), potentially implicating autophagy modulation in the immunological effects of FAO. Of note, CPT1A expression also appears to promote cancer cell resistance to CTL-derived IFNG by promoting antiapoptotic signaling (irrespective of changes in antigen presentation), at least in mouse melanoma B16 and mouse prostate cancer RM1 cells[64].

Apparently at odds with these observations, deletion of the FAO-relevant gene acetyl-CoA acetyltransferase 1 (*Acat1*) from mouse melanoma cells has been reported to compromise immune recognition and elimination, at least in part reflecting reduced expression of MHC Class I molecules on the cancer cell surface coupled with reduced T cell activation in the TME[65]. At least theoretically, such an apparent discrepancy may reflect the role of ACAT1 in cholesterol esterification[66], potentially leading to disruptions in plasma membrane lipid rafts associated with MHC molecules[67,68]. Despite this unknown, profiling the proteome of clinical samples from advanced stage melanoma patients undergoing either tumor infiltrating lymphocyte (TIL)-based or receiving an ICI specific for PD-1 revealed that proteomic signatures of lipid metabolism and OXPHOS to be enriched amongst responders[65]. It remains to be demonstrated whether these observations can be generalized to other tumor types.

Lipid mobilization upstream of FAO, as mediated by ADP ribosylation factor 1 (ARF1) has been implicated in the robust immunoevasive properties of cancer stem cells (CSCs). Specifically, *Arf1* deletion in a genetically engineered model of CRC has been shown to considerably slow down disease onset and progression as a consequence of the activation of immunogenic stress and death[15] in the CSC compartment, resulting in the DC-dependent activation of a tumor-targeting immune response[69].

Altogether, these observations exemplify the impact of FAO in cancer cells on the immunological contexture of the TME and cancer sensitivity to immunotherapy.

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Lipid synthesis.

Fatty acid synthase (FASN) is the rate-limiting enzyme of *de novo* lipid biosynthesis and its expression levels generally correlate with advanced cancer stage and metastatic dissemination[70]. In patients with ovarian carcinoma, high FASN levels are also associated with decreased T cell infiltration, owing not only T cell inhibition as directly mediate by the CD36-dependent uptake of fatty acids accumulating in the TME upon FASN overexpression[71,72], but also (1) to a lipid-driven defect of T cell cross-priming by DCs[73], as well as (2) to the ability of CD36 to promote T_{REG} cell functions[74]. In line with this notion, abundant tumor infiltration by CD36-expressing $CD8^+$ T cells has been associated with poor disease outcome in patients with NSCLC receiving immunogenic chemotherapy[75].

Eicosanoid synthesis.

Increased FASN activity also promotes the accumulation of intracellular lipid droplets that are associated with prostaglandin-endoperoxide synthase 2 (PTGS2, best known as COX2), a key enzyme in the synthesis of eicosanoids including prostaglandin E_2 (PGE_2)[76]. PGE_2 mediates direct mitogenic functions on malignant cells[77] as well as multipronged immunosuppressive effects that involve DC dysfunction as a consequence of prostaglandin E receptor 2 (PTGER2) and PTGER4 signaling coupled with intracellular cyclic AMP elevations[78,79], inhibition of NK cytotoxic and secretory activity (which also affect the recruitment of conventional type 1 DCs)[80], as well as T cell suppression upon the NF-κB-mediated upregulation of PD-1 (Ref. 81), an effect that is aggravated by the ability of PGE_2 to elicit the upregulation of PD-L1 on myeloid cells[82,83]. Of note, PGE_2 resembles hypoxia (which also has multipronged immunosuppressive effects, Box 3) in its ability to promote the upregulation of the ectonucleotidase 5'-nucleotidase ecto (5NTE, best known as CD73) on myeloid cells of the TME[84], which contributes to the immunosuppressive effects of nucleotide metabolism (see below). Interestingly, MFSD2 lysolipid transporter A, lysophospholipid (MFSD2A) has been shown to operate as an endogenous COX2 inhibitor in human and mouse gastric cancer cells, resulting in suppressed release of PGE_2 and the immunosuppressive cytokine transforming growth factor beta 1 (TGFB1)[85]. In this setting, MFSD2A overexpression by malignant cells has been shown to circumvent resistance to PD-1 inhibition along with signs of improved $CD8^+$ CTL reactivity in the TME[85].

Collectively, these observations highlight the complex interplay between fatty acid metabolism and immune cell function in the TME. An improved understanding of these mechanisms will provide valuable insights for the development of novel therapeutic strategies to enhance the efficacy of immunotherapy.

Other metabolic pathways

Additional metabolic circuitries that are altered along with malignant transformation have been shown to influence anticancer immunosurveillance. These include (but are not limited to) the biochemical cascades involved in the metabolism of nucleotides and various amino acids (Fig. 3).

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Nucleotides.

Cancer cells exhibit increased nucleotide synthesis as compared to their normal counterparts, and this has a considerable impact on anticancer immunity[86]. For instance, alterations of **urea cycle** enzymes reportedly lead to so-called "urea cycle dysregulation" (UCD), which redirects nitrogen flux toward carbamoyl-phosphate synthetase 2, aspartate transcarbamylase, and dihydrooratase (CAD)[87]. This results in excess pyrimidine synthesis promoting a distinctive genomic signature that is characterized by R→Y transversions and is associated with an increase in hydrophobic tumor antigens linked to improved sensitivity to ICIs in patients with melanoma[87]. Similar findings were obtained in preclinical models of CRC driven into the UCD by the depletion of argininosuccinate synthase 1 (ASS1)[87]. Moreover, the release of nucleotides by stressed and dying malignant cells has a major impact on the immunological contexture of the TME and the immunological reaction to cancer cell death[15]. For instance, extracellular ATP can be detected by myeloid cells including DCs and their precursors via purinergic receptor P2Y2 (P2RY2), which promotes chemotaxis[88,89], hence attracting them to the proximity of dying cells[90], or purinergic receptor P2X 7 (P2RX7), which promotes DC activation via inflammasome signaling and interleukin 1 beta (IL1B, best known as IL-1β) secretion[91]. Such an immunostimulatory effect is actively counteracted by extracellular ATP degradation through the sequential activity of ectonucleoside triphosphate diphosphohydrolase 1 (ENTPD1, best known as CD39) and CD73, which collectively promote the generation of adenosine, which has a potent and multipronged immunosuppressive activity[92,93]. Thus, intratumoral levels of CD39 and CD73 (which exhibit considerable variations not only across different neoplasms, but also in distinct cellular compartments of a the same tumor) are critical determinants of the immunostimulatory (low CD39 and CD73 expression) *vs* immunosuppressive (high CD39 and CD73 expression) effects of extracellular ATP[93].

Collectively, these observations point to the possibility to target nucleotide metabolism in cancer cells to achieve immunotherapeutic effects, an approach that is being investigated in clinical trials with promising results (see below).

Glutamine.

Microenvironmental glutamine represents an important source of energy and intermediate metabolites for rapidly proliferating cancer cells and immune cells[94]. In line with this notion, most cancer cells consume glutamine at a high rate relative to glucose and exhibit at least some degree of non-oncogene addiction to glutamine availability[21]. Suggesting an immunosuppressive function for this metabolic adaptation, human basal-like breast cancers exhibiting high transcriptional signatures of glutamine metabolism appear to be characterized by a scarce immune infiltrate, which correlates with poor disease outcome[95]. Accordingly, deletion of glutaminase (*Gls*) – which encodes the first enzyme of glutamine catabolism – in mouse TNBC cells has been shown to promote in vivo tumor control by a T cell-dependent mechanism[95]. Of note, pharmacological inhibition of GLS by a pro-drug that is preferentially activated in the TME (*i.e.*, JHU083) appears to drive potent anticancer responses in mice bearing MC38 CRCs by suppressing oxidative and glycolytic metabolism in cancer cells, but at the same time promoting OXPHOS and hence eliciting a long-lasting activated phenotype in CTLs[96]. These findings point to the existence of

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therapeutic strategies that efficiently target glutamine metabolism in cancer cells while sparing intratumoral CTLs. Glutamine metabolism in cancer cells also influences myeloid cells recruitment and activation. For instance, inhibiting GLS with a pharmacological agent has been reported to limit tumor infiltration by MDSCs and to favor to repolarization of TAMs toward an immunostimulatory "M1-like" profile in preclinical models of TNBC[97]. At least partially, this originated from the downregulation of indoleamine 2,3-dioxygenase 1 (IDO1) in malignant (and immune) cells, leading to a marked decrease in the abundance of immunosuppressive kynurenine[97]. Moreover, malignant cells appear to compete with type I conventional DCs (cDC1s) – which are key for antigen cross-presentation to T cells – for intratumoral glutamine availability via solute carrier family 38 member 2 (SLC38A2), at least in mouse models of melanoma and CRC[98]. These findings point to SLC38A2 on neoplastic cells as a potential target for the development of novel (immuno)therapeutic agents against cancer. Finally, increased glutamine uptake by cancer cells via solute carrier family 7 member 8 (SLC7A8, best known as LAT2) has been associated with CD47 upregulation in preclinical osteosarcoma models, resulting in inhibited phagocytosis and accelerated tumor progression[99]. Taken together, these findings exemplify the multipronged immunomodulatory functions of glutamine metabolism in cancer and immune cells.

Methionine.

Methionine is an essential amino acid that – besides contributing to protein synthesis – in involved in enzymatic methylation reactions[100]. Elevated levels of methionine-recycling enzymes and their products including 5-methylthioadenosine (MTA) and S-adenosylmethionine (SAM) have been linked to T cell exhaustion in mouse and human models of HCC[101]. In this setting, deletion of methionine adenosyltransferase 2A (*Mat2a*), which encodes a key enzyme in SAM synthesis, resulted in restored T cell activation and *in vivo* HCC control[101]. Along similar lines, methionine has been shown to impair CGAS activity in a methylation-dependent manner[102]. Of note, cancer cells generally express high levels of the methionine transporter solute carrier family 43 member 2 (SLC43A2, best known as LAT4), hence competing with T cells for this essential amino acid[103]. This results in the loss of demethylation of histone H3 at lysine 79 (H3K79me2), reduced signal transducer and activator of transcription 5A (STAT5) signaling and suppressed T cell functions[103]. Both LAT4 inhibition and methionine supplementation have been shown to circumvent this defect and restore anticancer immunity in mice bearing CRCs[103]. Tumor-specific LAT4 inhibition coupled with STING1 activation as achieved by a bimetallic nanoplatform bearing a *SLC43A2*-targeting CRISP/Cas9 construct plus Zn^{2+} ions has also been shown to mediate promising immunotherapeutic effects in preclinical TNBC models[104]. These examples point to the LAT4 as a potential target for the development of novel immunostimulatory agents with clinical applications. In this context, targeted approaches must be envisioned to enable the selective depletion of methionine from cancer cells[102,105], but not immune cells, which also heavily rely on methionine uptake for their anticancer function[103].

Tryptophan.

Tryptophan catabolism initiated by the enzymes indoleamine 2,3-dioxygenase 1 (IDO1) and tryptophan 2,3-dioxygenase (TDO) has attracted considerable attention as a potential target for the development of novel immunotherapeutic strategies[106]. IDO1 hyperactivation as occurring in some malignant cells (as well as in tolerogenic DCs) mediates indeed multipronged immunosuppressive effects that largely originate from the accumulation of kynurenine, which (amongst other activities) potently inhibits T cells[107] and promotes T_{REG} cell differentiation[108]. Indeed, while tryptophan is an essential amino acid, its concentration does not fall below a limiting threshold in the TME[109], implying that tryptophan shortage does not contribute to IDO1-driven immunosuppression as initially proposed[110]. Additional immunosuppressive products of the IDO1 pathway include quinolinic acid, which has been shown to promote M2-like TAM polarization downstream of forkhead box O1 (FOXO1) and peroxisome proliferator activated receptor gamma (PPARG) signaling in the GBM setting[111].

Lysine.

GBM stem cells have been shown to reprogram lysine catabolism, resulting in an intracellular accumulation of crotonyl-CoA and consequent histone H4 lysine **crotonylation**[112]. In this context, inhibition of lysine crotonylation enhances type I IFN signaling elicited by double stranded RNA (dsRNA) and dsDNA, culminating with restored $CD8^+$ T cell infiltration, and impaired disease progression[112]. These data point to lysine metabolism as a potential target for the development of novel immunotherapies. Whether this mechanism is operational in cancer types other than GBM, though, remains unclear.

Targeting metabolic cancer vulnerabilities to restore immunosurveillance

The development of small molecules and monoclonal antibodies targeting cancer metabolism has been initiated decades ago, including various agents that are currently under clinical evaluation[113]. Accumulating data indicate that at least some of these agents represent promising tools to restore cancer immunosurveillance and increase tumor sensitivity to approved cancer therapeutics that engage anticancer immunity, including not only immunotherapy, but also immunogenic chemotherapy[114], some targeted anticancer agents[115], and radiotherapy (at least when used focally and according to specific dose and fractionation protocols)[116]. Importantly, a number of dietary interventions are also being investigated for their ability to alter cancer cell metabolism in support of enhanced anticancer immunity, but owing to space limitations they are not further discussed here (Supplemental Information).

Glucose and lactate.

Pharmacological GLUT1 inhibition with BAY-876 has been harnessed for increasing therapeutic responses to an ICI targeting PD-1 in preclinical models of pancreatic and lung cancer[25]. In this setting though, solute carrier family 2 member 3 (SLC2A3, best known as GLUT3) overexpression appeared to compensate (at least in part) for GLUT1 inhibition[25], pointing to dual GLUT1/GLUT3 inhibition as a potentially superior strategy. PD-1 blockage has been shown to synergize with PKF-015, a pharmacological inhibitor of the glycolytic enzyme 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3), in mouse models of melanoma and colorectal carcinoma (CRC), an effect that could be attributed to the ability of PFKFB3 inhibition to elicit PD-L1 expression[117]. Preliminary

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results from a dose-escalation Phase I clinical trial testing a PKF-015 analog in patients with solid tumors (NCT02044861) confirmed the feasibility of this approach[118]. That said, targeting glucose uptake or consumption for cancer therapy remains challenging as multiple healthy cells including neurons abundantly rely on glucose metabolism for their normal functions, calling for the development of targeted delivery strategies. At least theoretically, inhibiting lactate secretion or uptake in the TME may present less challenges than blocking glycolytic metabolism as a whole. However, past drug development efforts focused on lactate, including the development of the MCT1 inhibitor AZD3965 (which demonstrated a good tolerability in patients with advanced solid tumors)[119] have been discontinued. Whether recent preclinical findings demonstrating a positive interaction of multiple lactate-targeting strategies including MCT4 inhibitors with various forms of immunotherapy[120,121] will reinvigorate these efforts remains unclear.

Glutamine.

Telaglenastat (a GLS-targeting agent also known as CB-839) has been reported to synergize with radiotherapy (which can mediate robust immunostimulatory effects)[122,123] against human HNSCC and NSCLC xenografts[124,125]. Whether such a radiosensitizing effect involved any degree of innate immune activation, however, remains unclear. That said, telaglenastat has also been shown to synergize with CTLA4 and PD-1 blockers in immunocompetent models of melanoma[126], suggesting that this agent mediates indeed therapeutically relevant immunostimulatory effects. Irrespective of this unresolved possibility, clinical data from a few independent studies in patients with metastatic renal cell carcinoma suggest that telaglenastat can be safely combined with standard-of-care chemotherapy in this patient population, although with minimal therapeutic benefits[127–129]. These clinical findings considered reduced the interest in the development of telaglenastat as a novel anticancer agent, with only one study in patients with NSCLC remaining open for recruitment as of Feb 2024 (NCT03831932, source www.clinicaltrials.gov).

Pharmacological inhibition of glutamine uptake via LAT2 with BCH 2-aminobicyclo-(2,2,1)-heptane-2-carboxylic acid has been shown to enhance the therapeutic effect of the immunogenic chemotherapeutic doxorubicin against osteosarcoma cells, an effect that at least partially reflected CD47 downregulation and restored cancer cell phagocytosis[99]. Along similar lines, V-9302, a pharmacological inhibitor of glutamine uptake, has been shown to mediate T cell-dependent tumor control in preclinical models of TNBC[95]. That said, V-9302 administration to mouse lung cancer and CRC cells has also been associated with PD-L1 upregulation via NF-κB, *de facto* suppressing tumor-targeting immune responses[130]. Such an immunosuppressive response, however, was accompanied by the upregulation of Fas cell surface death receptor (FAS)[131] on malignant cells, rendering them more sensitive to T cell responses as pharmacologically reactivated with a PD-L1 blocker[130]. Whether these apparently discrepant observations reflect specificities of glutamine metabolism in different cancer cell types remains to be clarified.

Tryptophan.

Preclinical data generated in a large panel of immunocompetent tumor models demonstrate that pharmacologically or genetically blocking IDO1 and/or TDO activity promotes robust

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immunotherapeutic effects that can generally be amplified with ICIs[132,133] These findings spurred considerable interest in the development of clinically testable IDO1 inhibitors such as epacadostat[134]. Preliminary findings from non-randomized early phase clinical trials suggested that epacadostat can be safely and effectively combined with PD-1 blockers in patients with advanced solid tumors[135]. However, despite considerable expectations, a randomized Phase III clinical study enrolling subject with advanced melanoma demonstrated no therapeutic advantages for epacadostat plus the PD-blocker pembrolizumab over pembrolizumab alone[136]. Whether this reflects the existence of alternative tryptophan degradation pathways that have been shown to mediate immunosuppressive effects in non-oncological settings (notably autoimmune disorders)[137] and may be upregulated in the context of IDO1 inhibition remains to be demonstrated. Obviously, these negative results considerably decreased the interest of pharma companies to develop IDO1 inhibitors[138], with only few clinical trials still open to recruitment as of Feb 2021 (source www.clinicaltrials.gov). Whether novel approaches targeting IDO1 such as the inhibition of ubiquitin specific peptidase 14 (USP14), which effectively restores T cell-dependent disease control in preclinical models of CRC[139], will reinvigorate such interest remains unclear.

Nucleotides.—Standalone pharmacological inhibition of CD39, CD73 and/or adenosine receptors have all been associated with restored anticancer immunity and improved disease control in a variety of preclinical cancer models[140–142]. Moreover, the small CD73-targeting molecule AB680 reportedly sensitize mouse pancreatic carcinoma to ICIs specific for PD-1, a therapeutic effect reflecting decreased tumor infiltration by T_{REG} cells[143]. Along similar lines, a monoclonal antibody targeting CD73 has been reported to improve the therapeutic effects of focal radiotherapy combined with a CTLA4 blocker in preclinical models of breast cancer, at least partially reflecting superior DC recruitment to the TME and activation[144]. Similar results have been obtained by combining pegylated adenosine deaminase (ADA), which converts extracellular adenosine into inosine, with a PD-1 blocker in preclinical models of TNBC and pancreatic carcinoma[84]. Finally, adenosine A2a receptor (ADORA2A) antagonists have been shown to positively cooperate with several immunotherapeutic strategies in preclinical tumor models, including (but not limited to) CAR T cell therapies in leukemia models[145] as well as PD-1 blockers in models of breast cancer and melanoma[146,147]. In line with these preclinical findings, various phase I clinical trials have evaluated ADORA2A or ADORA2B antagonists in patients with CRC, NSCLC and castration-resistant prostate cancer with encouraging results[148,149]. Moreover, two parallel Phase II studies reported promising activity for a monoclonal antibody neutralizing CD73 (*i.e.*, oleclumab) in combination with the PD-L1 blocker durvalumab delivered as neoadjuvant interventions to patients with operable NSCLC[150] or as part of the management of unresectable NSCLC[151]. Conversely, while numerous studies have evaluated and are evaluating CD39 blockers in patients with cancer (source www.clinicaltrials.gov), the clinical applicability of this approach remains uncertain.

Fatty acids.

Inhibiting FAO via the carnitine palmitotransferase 1 (CPT1) blocker etomoxir reportedly synergizes with CD47-targeting antibodies and radiotherapy against otherwise radioresistant mouse GBMs established intracranially, along with the restoration of macrophage-dependent

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cancer cell phagocytosis[62]. Whether these findings can be translated to human GBM, however, remains unclear. Pharmacological inhibition of FASN with cerulenin has been shown to restore DC activation and tumor infiltration by effector T lymphocytes coupled with at least partial tumor control in preclinical models of ovarian cancer[73]. In line with these findings, the FASN inhibitor denifanstat (also known as TVB-2640) has been shown to be well tolerated in patients with advanced tumors[152] and high-grade astrocytoma[153], prompting the initiation of clinical trials in patients with various neoplastic conditions (NCT02980029; NCT03179904; NCT03808558; NCT05743621). CD36 blockers have also demonstrated promising activity in combination with immunogenic immunotherapy in preclinical models of pancreatic cancer[154] as well as in combination with PD-1 blockers in preclinical models of melanoma[74], but their development into clinically available drugs is still in its infancy, with only one agent (*i.e.*, VT1021) being under evaluation for the treatment of GBM (NCT03970447).

Eicosanoids.

Corroborating the ability of PGE_2 to potently suppress anticancer immune responses, pharmacological strategies for the inhibition of COX2, PTGER2 or PTGER4 have been associated with improved tumor control along with restored immune effector functions and positive cooperativity with ICIs in multiple preclinical tumor models, including models of CRC, melanoma, breast cancer and NSCLC[78,79,155–157]. Since agonists of the so-called liver X receptors (LXRs) have been demonstrated to promote MFSD2A expression[158,159], these agents might provide an appealing tool to limit COX2-dependent immunosuppression. However, recent evidence indicates that LXR activation also results in the expression of sphingomyelin phosphodiesterase acid like 3A (SMPDL3A), which actively degrades the CGAS product 2′3′-cyclic GMP-AMP (cGAMP) to suppress STING1 activation, at least in myeloid cells[160]. Along similar lines, conventional COX2 inhibitors including celecoxib and aspirin mediate multipronged immunosuppressive effects encompassing direct CGAS inhibition[161]. Thus, the restoration of optimal anticancer immunity by PGE_2-directed strategies may benefit from agents that antagonize PGE_2 receptors such as PTGER2 and PTGER4. Along these lines, TPST-1495 (a novel dual antagonist of PTGER2 and PTGER4) is currently being investigated as standalone therapeutic agent of in combination with pembrolizumab in patients with advanced solid tumors (NCT04344795). Additional trials testing celecoxib plus pembrolizumab in patients with colorectal or rectal cancer are also underway (NCT03638297, NCT03926338, NCT05731726), largely based on the proven oncopreventive effects of COX2 inhibitors in this oncological indication[162]. Based on the aforementioned considerations, it will be interesting to see these studies will document any degree of cooperativity between COX2 inhibition and PD-1 blockers.

These findings collectively emphasize the potential of metabolic inhibitors not only as cancer-targeted drugs, but also as immunostimulants that may synergize with other therapeutic strategies that restore immunosurveillance (Table 1).

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Concluding remarks

The term "immunometabolism" has recently been coined to refer to the metabolic configuration of immune cells, which – perhaps not surprisingly – is very dynamic, critical for immune effector functions, and extremely sensitive to microenvironmental cues[16–18]. The abundance and function of tumor-infiltrating immune cells is also influenced by the metabolic alterations that accompany malignant transformation and tumor progression, as discussed herein. Importantly, while multiple clinically relevant agents have been shown to mediate immunostimulatory effects[114–116], the potential contribution of altered cancer cell metabolism to immunostimulation has generally been overlooked.

An expanding preclinical literature points indeed to the possibility of targeting cancer cell metabolism to achieve immunostimulatory effects that can be maximized with various forms of immunotherapy, notably ICIs. The clinical translation of this paradigm, however, presents multiple challenges. First, most metabolic modulators developed so far exhibit limited (if any) specificity for cancer cells, implying that they may be toxic for healthy tissues and/or directly impair immune functions[9]. This calls for the development of strategies for the targeted delivery of metabolic inhibitors to malignant cells, such as drug-containing liposomes expressing one or more ligands for cancer cell receptors, or drug-associated nanoparticles with physicochemical features that promote their selective uptake by cancer cells[163]. Second, while modern omics technologies may be harnessed to investigate potentially actionable metabolic liabilities in diagnostic biopsies, several therapeutics commonly employed in clinical cancer management have major metabolic consequences, either by directly promoting a metabolic rewiring in malignant cells[164], or indirectly by favoring the selection of neoplastic cells with specific metabolic traits[165], often in the context of extensive intratumoral heterogeneity[6]. In this respect, it will be important to acquire as much information as possible on the metabolic changes imposed by conventional therapies and their immunomodulatory correlates from pre- and post-treatment biopsies (for instance by longitudinal monitoring of intratumoral metabolites in the setting of window-of-opportunity clinical trials). Third, the vast majority of current preclinical tumor models fail to recapitulate the metabolic and immunological heterogeneity of human neoplasms[166]. With all limitations that apply[167], we surmise that humanized mice hosting non-dissociated patient-derived material and colonized with patient-derived hemopoietic precursors may at least partially circumvent such issue. Finally, a number of host-related factors have been shown to influence cancer cell metabolism and/or immune functions, including not only fairly obvious systemic conditions such as obesity and diabetes[168], but also less recognizable variables such as the abundance and composition of the intratumoral and intestinal microbiome[169]. Additional work is needed to mechanistically decipher the intricate links between these factors, cancer cell metabolism and tumor-targeting immunity.

Despite these and other challenges, cancer cell metabolism stands out as a promising target to restore immunosurveillance and hence convert immunologically cold tumors into hot lesions that respond to immunotherapy.

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Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Glossary

Catabolism

Set of metabolic pathways that breakdown large molecules into smaller units for recycling or ATP production purposes

Anabolism

Set of metabolic pathways that build large molecules from smaller units in support of cell growth and proliferation

OXPHOS

Mitochondrial pathway that generates ATP from a series of oxidation reactions that culminate with the generation of H_2O

TCA cycle

Mitochondrial circuitry that ensure adequate levels of key metabolites involved in several catabolic and anabolic reactions

PPP

Metabolic shunt that diverts glycolytic intermediates towards the synthesis of nucleotides, some amino acids and antioxidants

Lactylation

Post-translational modification of lysine residues by lactate

***De novo* lipid biosynthesis**

Metabolic cascade converting acetyl-CoA into long-chain lipids for cellular anabolism

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Urea cycle

Metabolic pathway to convert excess ammonia into urea for excretion

Crotonylation

Post-translational modification of lysine residues by crotonyl-CoA

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Box 1.

Influence of cancer cell metabolism on the tumor stroma.

Malignant lesions developed in the context of an intimate crosstalk with stromal cells including cancer-associated fibroblasts (CAFs) that exhibits a considerable metabolic component. For instance, ovarian cancer cells have been shown to supply lactate and glutamate to CAFs, hence fostering the synthesis and release of glutamine by CAFs in support of their own proliferation[173]. A similar mechanism also appears to be operational in prostate cancer models[174]. Along similar lines, pancreatic cancer cells have been reported to promote autophagic responses in stromal pancreatic stellate cells, resulting in a local release of alanine that relieves the malignant cell dependency on glucose and serum-derived nutrients for proliferation[175]. Moreover, pancreatic cancer cells can reportedly harness proline derived from the breakdown of CAF-produced collagen to survive under nutrient-limited conditions[176], highlighting yet another metabolic circuitry connecting malignant cells and their stroma. To which extent proline secreted by CAFs to accommodate redox stress as induced by transforming growth factor beta 1 (TGFB1) signaling[177] contributes to cancer cell survival, however, remains to be demonstrated. Importantly, other stromal cells have also been shown to support cancer cell proliferation via metabolic circuitries. For instance, fatty acid binding protein 4 (FABP4) expression in ovarian cancer cells appears to underlie a mechanism that promote lipolysis in cancer-associated adipocytes. This results in the secretion of fatty acids that are avidly taken up by malignant cells and used for bioenergetic purposes via fatty acid oxidation[178]. Collectively, these observations nicely exemplify the existence of multiple metabolic exchanges between neoplastic cells and non-transformed components of the tumor microenvironment, notably stromal cells.

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Box 2.

Autophagic responses in cancer cells and tumor-targeting immunity.

Autophagy is a lysosome-dependent catabolic mechanisms that dispose of potentially cytotoxic and/or dysfunctional cytoplasmic entities (*e.g.*, permeabilized mitochondria)[179]. Autophagy serves major homeostatic and metabolic functions in all nucleated cells, *de facto* supporting the differentiation and functions of numerous immune cell types[180]. Moreover, both natural and therapy-driven autophagic responses in malignant cells have been shown to influence tumor-targeting immune responses via multiple, context-dependent mechanisms. On the one hand, autophagic responses as driven by immunogenic chemotherapy have been shown to be required for the optimal release of ATP by dying cells[140], hence orchestrating the recruitment and activation of dendritic cells (DCs) and ultimately promoting $CD8^+$ cytotoxic T lymphocyte (CTL)-dependent anticancer immunity. On the other hand, autophagy has been reported to mediate robust immunosuppressive effects including: (1) the inhibition of type I interferon (IFN) responses as elicited in malignant cells by radiotherapy or as driven spontaneously in neoplasms with elevated mutational burden, resulting in limited cell death adjuvanticity and hence preferential tumor infiltration by regulatory T (T_{REG}) cells coupled with CTL exhaustion[170,172], (2) the inhibition of MHC Class I molecule exposure on the cancer cell surface, resulting in reduced antigenicity[171], and (3) the degradation of natural killer (NK)-produced granzyme B (GZMB), resulting in limited susceptibility to lysis by immune effector cells[181]. Thus, autophagic responses in malignant cells stand out as central regulators of all aspects of anticancer immunity. That said, the development of pharmacological modulators of autophagy present multiple challenges that have not been successfully addressed yet[182,183].

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Box 3.

Microenvironmental hypoxia and tumor-targeting immunity.

Solid tumors are often characterized by at least some areas where oxygen tension falls below physiological values[184]. Malignant cells adapt to these abnormal metabolic conditions by a variety of mechanisms that are often orchestrated by the transcriptional regulator hypoxia inducible factor 1 subunit alpha (HIF1A)[184]. The major metabolic shift imposed by HIF1A involves the redirection of glucose flux from oxidative phosphorylation (OXPHOS) to anaerobic glycolysis coupled with abundant lactate secretion[184], which has major immunosuppressive effects (see main text). Moreover, HIF1A promotes the upregulation of vascular endothelial growth factor A (VEGFA), which besides promoting neoangiogenesis supports the accumulation and immunosuppressive activity of $CD4^+CD25^+FOXP3^+$ regulatory T (T_{REG}) cells[185]. Moreover, HIF1A promotes immunosuppressive nucleotide metabolism (see main text) by upregulating not only ectonucleoside triphosphate diphosphohydrolase 1 (ENTPD1, best known as CD39) and ectonucleotidase 5'-nucleotidase ecto (5NTE, best known as CD73), hence resulting in accelerated extracellular ATP degradation, but also adenosine A2a receptor (ADORA2A) and ADORA2B, further fostering adenosinergic signaling[186]. Of note, hypoxia also mediate immunosuppressive effects that do not directly involve cancer cell metabolism, including the activation of a CD39-dependent exhaustion program in tumor-infiltrating T lymphocytes[187], the repolarization of tumor-associated macrophages (TAMs) towards an M2-like state[188], and the elimination of tumor-targeting γδ T cells[189]. Thus, hypoxia represent a major driver of immunosuppression in the tumor microenvironment,

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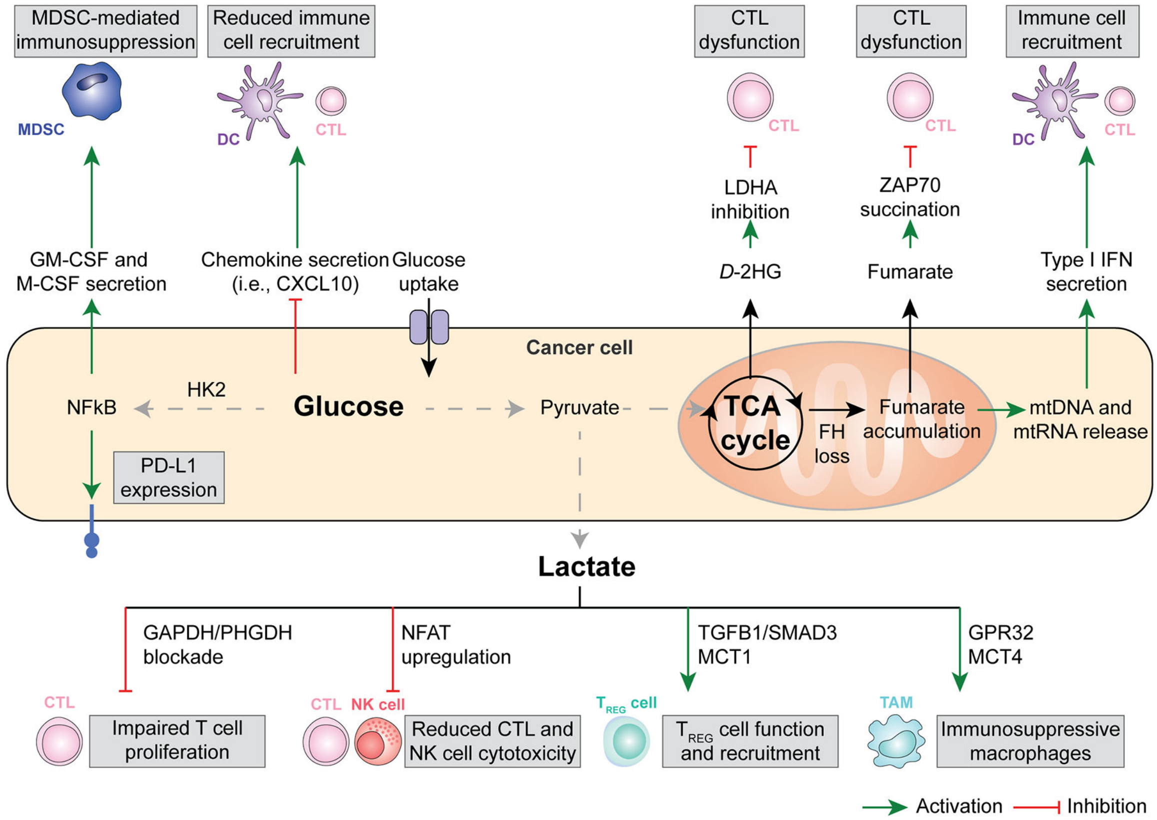

Figure 1. Glucose, lactate, and intermediate metabolism in anticancer immunity.

The bioenergetic metabolism of cancer cells, characterized by increased glucose uptake coupled with abundant lactate secretion as well as alterations in the tricarboxylic acid (TCA) cycle has a major impact on the immunological tumor microenvironment (TME). For instance, an increased glycolytic flux in cancer cells has been associated with the NF-κB-dependent upregulation of PD-L1 and the secretion of myeloid-derived suppressor cell (MDSC)-recruiting cytokines like GM-CSF and M-CSF, as well as with the reduced release of the cytotoxic T lymphocyte (CTLs)-recruiting and pro-inflammatory chemokine CXCL10. Along similar lines, microenvironmental lactate has been shown to limit the proliferation and activation of CTLs and natural killer (NK) cells while promoting the recruitment and immunosuppressive function of regulatory T (T_{REG}) cells and tumor-associated macrophages (TAMs). Finally, mitochondrial alterations emerging from TCA cycle defects have been linked with the secretion of metabolic intermediates with direct CTL-suppressive effects, including fumarate and *D*-2-hydroxyglutarate (*D*-2HG), as well as with the cytosolic accumulation of cytosolic mitochondrial DNA (mtDNA) and mitochondrial RNA (mtRNA), instead culminating with the secretion of immunostimulatory type I interferon (IFN). DC, dendritic cell.

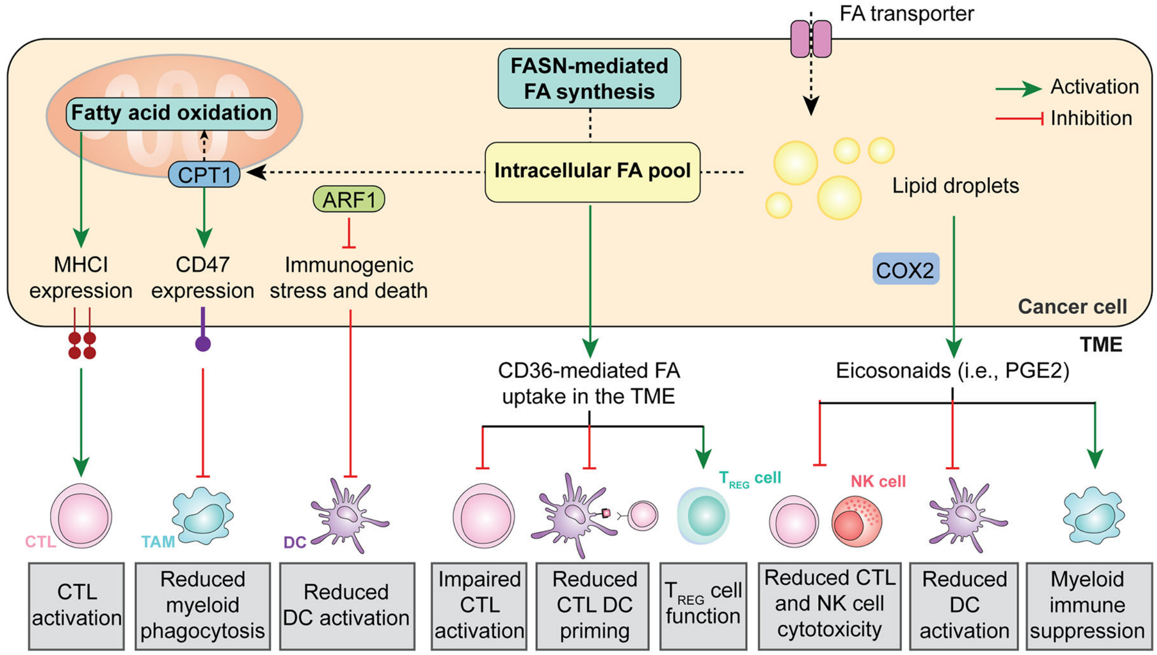

Figure 2. Fatty acid and eicosanoid metabolism on anticancer immunity.

Cancer cells generally exhibit an increase in both fatty acid (FA) intake from the tumor microenvironment (TME) and endogenous fatty acid synthesis. This results in immunomodulatory effects emerging from (1) increased MHC Class I exposure on the cancer cell surface, resulting in improve recognition by cytotoxic T lymphocytes (CTLs), (2) elevated CD47 expression, limiting phagocytic uptake by myeloid cells; and (3) inhibited immunogenic cell death (ICD), preventing pronounced dendritic cell (DC) activation. Moreover, high levels of FAs in the TME have a direct immunosuppressive effect on CTLs and DCs, coupled with an increased in regulatory T (T_{REG})-mediated immunosuppression. Finally, cancer cells can convert FAs stored as lipid droplets into immunosuppressive eicosanoids such as prostaglandin E2 (PGE_2). NK, natural killer.

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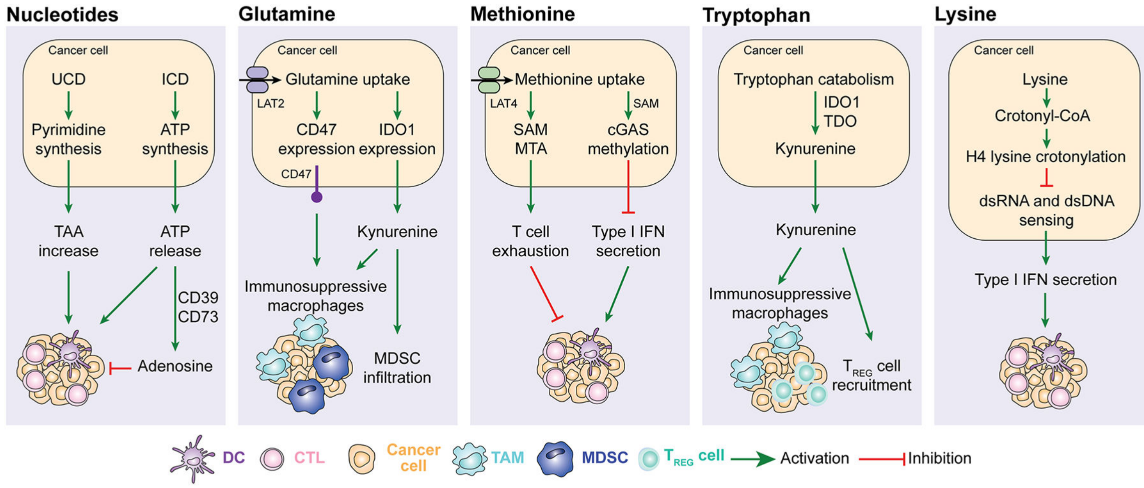

Figure 3. Nucleotide and amino acid metabolism in anticancer immunity.

Alterations in the urea cycle promote cancer cell immunogenicity by favoring the expression of tumor-associated antigens (TAA), while ATP released in the context of immunogenic cell death (ICD) mediates potent chemotactic and immunostimulatory effects on myeloid cells that are actively counteracted when extracellular ATP is converted into immunosuppressive adenosine by CD39 and CD73. Increased glutamine metabolism favors the accumulation of immunosuppressive tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs) by promoting CD47 and IDO1 upregulation. Methionine uptake by cancer cells promotes cytotoxic T lymphocyte (CTL) exhaustion via 5-methylthioadenosine (MTA) and S-adenosylmethionine (SAM) as it inhibits type I interferon (IFN) secretion by methylating CGAS. Tryptophan degradation as mediated in cancer cells and myeloid cells by IDO1 results in the accumulation of immunosuppressive metabolites including kynurenine. Finally, lysine has been shown to suppress type I IFN production by malignant cells upon histone H4 lysine crotonylation. DC, dendritic cell; T_{REG}, regulatory T; UCD, urea cycle dysregulation.

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Table 1.

Metabolic inhibitors targeting cancer cells to restore immunosurveillance*

Vulnerability	Target	Drug	Phase**	Indication(s)	Notes	In clinical development***	Ref.
Adenosine	Adenosine	PEG-ADA	Preclinical	Breast cancer Melanoma Lung cancer	Combined with ICIs	N	84
Adenosine	ADORA2A	AZD4635	Phase Ia/Ib	Solid tumors	Combined with a PD-L1 blocker	Y	NCT02740985 149
Adenosine	ADORA2A	SCH58261	Preclinical	Breast cancer Melanoma	Combined with CAR T cells or ICIs	N	145 147
Adenosine	ADORA2A	Taminadenant	Phase I	NSCLC	Combined with a PD-1 blocker	Y	NCT02403193 148
Adenosine	CD73	Oleclumab	Phase II	NSCLC	Combined with a PD-L1 blocker	Y	NCT03794544 NCT03822351 150 151
Eicosanoids	COX2	Celecoxib	Phase II	CRC	Combined with a PD-1 blocker	Y	NCT03638297 NCT03926338 NCT05731726
Eicosanoids	PTGER2	PF-04418948	Preclinical	CRC TNBC	Combined with a PD-1 blocker	N	79
Eicosanoids	PTGER2 PTGER4	TPST-1495	Phase Ia/Ib	Solid tumors	Combined with a PD-1 blocker	Y	NCT04344795
Eicosanoids	PTGER4	L161,982	Preclinical	CRC TNBC	Combined with a PD-1 blocker	N	79
Eicosanoids	PTGER4	MF-766	Preclinical	Brest cancer CRC	Combined with a PD-1 blocker	N	156
Fatty acids	CD36	CD36 blockers	Preclinical	Melanoma Pancreatic cancer	Optionally combined with ICIs	N	74 154
Fatty acids	FAO	Etomoxir	Preclinical	Glioblastoma	Combined with a CD47 blocker	N	62
Fatty acids	FASN	Cerulenin	Preclinical	Ovarian cancer	Improved disease control coupled with signs or restored immunity	N	73
Fatty acids	FASN	Denifanstat	Phase II	Astrocytoma $HER2^{+}$ breast cancer NSCLC	Combined with disease-specific SOC chemotherapy	Y	NCT03032484 NCT03179904 NCT03808558 153
Fatty acids	THBS1	VT1021	Phase II/III	Glioblastoma	Compared to SOC chemotherapy	Y	NCT03970447

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Vulnerability	Target	Drug	Phase**	Indication(s)	Notes	In clinical development***	Ref.
Glucose	GLUT1	BAY-876	Preclinical	Lung cancer Pancreatic cancer	Combined with ICIs	N	25
Glucose	PFKFB3	PKF-015	Phase I	Solid tumors	Dose-escalation study	N	NCT02044861 118
Glutamine	ASCT2	V-9302	Preclinical	CRC Lung cancer TNBC	Optionally combined with a PD-1 blocker	N	95 130 131
Glutamine	GLS	Telaglenastat	Phase II	Renal cell carcinoma	Combined with SOC chemotherapy	Y	NCT03163667 NCT03428217 NCT03831932 127 128 129
Glutamine	LAT2	BCH	Preclinical	Osteosarcoma	Combined with a CD47 blocker	N	99
Lactate	MCT1	AZD3965	Phase I	Solid tumors	Dose-escalation study	N	NCT01791595 119
Lactate	MCT4	MSC-4381	Preclinical	Solid tumors	Combined with ICIs	N	120
Tryptophan	IDO1	Epacadostat	Phase III	Melanoma	Combined with a PD-1 blocker	N	NCT02752074 136
Tryptophan	IDO1	IU1	Preclinical	CRC	Combined with a PD-1 blocker	N	139

Abbreviations: BCH, 2-aminobicyclo-(2,2,1)-heptane-2-carboxylic acid; CRC, colorectal carcinoma; ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung carcinoma; PEG-ADA, PEGylated adenosine deaminase; SOC, standard of care; TNBC, triple negative breast cancer.

* Main examples;

** most advanced;

*** as of February 24, according to www.clinicaltrials.gov.