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Review article

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Metabolites as agents and targets for cancer immunotherapy

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Abstract

The depletion or accumulation of metabolites in the tumour microenvironment is one of the hallmarks of cancer, but targeting cancer cell metabolism therapeutically must also take into account the impact on metabolic pathways in immune cells. As we understand more about immunometabolism, opportunities arise for synergies between agents that modulate metabolism and immunotherapy. In this Review, we discuss the pivotal role of metabolic pathways in both cancer and immune cells in shaping the tumour microenvironment. We survey major anabolic and catabolic pathways and discuss how metabolic modulators and dietary nutrients can improve the anticancer immune response and overcome drug resistance mechanisms. Agents in the clinic include inhibitors of the adenosine and tryptophan pathways, and we discuss opportunities and challenges for successful drug development in the context of immune checkpoint blockade and chimeric antigen receptor (CAR)-T cell therapies.

Sections

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Introduction

In the past century, the isolation and study of natural metabolites has yielded clinical breakthroughs, as exemplified by antibiotics for the treatment of infectious diseases and chemotherapeutics as anticancer agents[1]. In 1948, inhibitors of folate metabolism were successfully used to treat patients with leukaemia, sparking interest in targeting tumour metabolism[2]. Along the same lines, synthetic compounds targeting nucleoside metabolism have also emerged as powerful chemotherapeutic drugs[2]. However, although these drugs are intended to target cancer cells, they damage immune cells, which reduces their therapeutic benefit[3]. This issue highlights the complexity of targeting metabolic pathways and the need to disentangle the metabolic pathways that affect cancer cells and those that affect immune cells.

Metabolism is a delicate balance between the degradation (catabolism) and generation (anabolism) of molecules required to maintain cellular functions[4]. In the context of cancer, increased proliferation of tumour cells inevitably amplifies energy usage, disrupting the local and sometimes the systemic balance of metabolites[5,6]. This imbalance creates an ever more challenging environment for immune cell function and therapeutic interventions. Adding complexity, tumours not only use more energy but often rewire their metabolism, most famously by increasing the glycolytic production of lactate even under aerobic conditions — a mechanism known as the Warburg effect[7]. However, increased glycolysis is only one of many cancer-relevant metabolic alterations, which also include the increased use of amino and fatty acids, as well as the secretion of oncometabolites such as 2-hydroxyglutarate[6]. Cancer cell growth tends to deplete the microenvironment of essential nutrients and to lead to accumulation of waste products including lactate[8]. At the same time, immune cells, particularly activated T cells, undergo metabolic reprogramming that enables their proliferation, cytokine production and acquisition of effector functions[9] (Box 1). The resulting metabolic competition between tumour and immune cells can lead to T cell exhaustion and immune evasion by the tumour[8]. Before the dawn of immunotherapy, a substantial number of metabolism-modulating agents were developed to target tumour cells, but with little regard to their effects on immune cells, which likely limited their clinical success. Since then, more-favourable immunomodulatory effects have been achieved by metabolic interventions designed to broaden and boost cancer immunotherapy effects[10].

In this Review, we discuss the therapeutic development of metabolites and inhibitors of metabolic pathways, while emphasizing attempts to improve cancer immunosurveillance. We focus in particular on amino acids, glycolysis, nucleosides and oxidative phosphorylation (OXPHOS), as well as on the microbial metabolites that are intertwined with nutrition. We discuss pathways that generate and degrade specific metabolites, as well as the cancer- and immune-related effects of these metabolites. We then describe strategies to promote or inhibit these metabolic pathways for cancer treatment, specifically emphasizing immune-related effects, as direct impacts on tumour cells have been extensively reviewed elsewhere[11].

The field of metabolic interventions has suffered major setbacks in recent years, as prominently exemplified by the resounding clinical failure of indoleamine 2,3-dioxygenase 1 (IDO1) inhibitors. However, recent preclinical and early clinical studies showcase how cellular metabolism offers promising targets to improve immunotherapy.

Amino acid metabolism

Amino acids are the building blocks of proteins, and metabolic competition between these metabolites is an important suppressive mechanism in tumours[5,6]. In addition, many non-proteinogenic amino acid derivatives have potent signalling and regulatory roles; for example, kynurenine or 2-hydroxyglutarate.

Tryptophan and kynurenine

As a precursor of the bioactive derivatives melatonin and serotonin, tryptophan is the least abundant essential amino acid and is implicated in many aspects of health and disease[12]. The metabolism of tryptophan begins with its conversion to *N*-formylkynurenine (NFK) by one of three enzymes: trpytophan-2,3-dioxygenase (TDO), IDO1 or IDO2 (ref. 12) (Fig. 1). NFK is metabolized to kynurenine by kynurenine formamidase and further degraded by four kynurenine aminotransferases into kynurenic acid, which constitutes a biomarker for multiple inflammatory and neurodegenerative diseases[12]. In cancer, several serum tryptophan metabolites were associated with poor prognosis in a randomized trial with stage III patients receiving a prophylactic dendritic cell vaccine[13]. Importantly, tryptophan depletion and kynurenine accumulation through IDO1 are established factors contributing to an immunosuppressive tumour microenvironment (TME)[14,15]. IDO1 is expressed by antigen-presenting cells (dendritic cells and macrophages) as well as by tumour cells and correlates with poor prognosis across many solid tumours[16–19]. In a key mechanism, kynurenine activates aryl hydrocarbon receptor (AHR), which induces differentiation of regulatory T cells (T_{reg} cells) and tumour infiltration by myeloid-derived suppressor cells (MDSCs)[20,21]. Similarly, TDO expression in human brain tumours is associated with kynurenine production, AHR activation and poor progression[22]. Kynurenine uptake by $CD8^+$ T cells via solute carrier family 7 member 8 (SLC7A8) and SLC36A4 (PAT4) results in AHR-dependent upregulation of the immune checkpoint receptor programmed cell death protein 1 (PD1), likely explaining why TDO inhibition synergizes with PD1 blockade in mouse cancer models[23,24]. Interestingly, continuous IL-2 exposure induces yet another tryptophan-degrading enzyme — tryptophan hydroxylase — in T cells, leading to 5-hydroxytryptophan accumulation, which activates AHR and thereby causes T cell exhaustion[25].

IDO1 inhibition has been found to boost antitumour responses in combination with chemotherapy and radiotherapy in murine models and canine malignancies[26–28]. Similarly, IDO1 knockout or an IDO1 inhibitor synergized with anti-cytotoxic T lymphocyte-associated protein 4 (CTLA4) immune checkpoint blockade (ICB) in the B16 murine melanoma model[29]. Based on the efficacy of IDO1 inhibition in preclinical models, IDO1 inhibitors, including epacadostat, BMS-986205 and navoximod, were developed and showed acceptable safety profiles in the clinic[14]. Epacadostat showed a promising objective response rate in combination with the PD1 inhibitor pembrolizumab in a phase I/II melanoma trial[30]. However, enthusiasm for IDO1 inhibitors was shattered by the disappointing results of a phase III trial evaluating epacadostat in combination with pembrolizumab in patients with advanced unresectable melanoma[31]. The addition of epacadostat did not improve survival over pembrolizumab alone, leading to the termination of two large phase III trials testing BMS-986205 in non-small-cell lung cancer (NSCLC) (NCT03417037) and head and-neck cancer (NCT03386838; Table 1 and Supplementary Table 1). Similarly, a recently completed phase III trial combining epacadostat with pembrolizumab in metastatic renal cell carcinoma (RCC) showed no benefit of adding epacadostat (NCT03260894)[32]. A similar trial focusing on metastatic head and neck squamous cell carcinoma hinted at a slight potential benefit (NCT03358472). Overall, the development of IDO1 inhibitors was severely impacted by these deceptive clinical data.

Box 1 | T cell metabolism

T cells are a crucial component of the antitumour immune response, and reviving T cell activity is a key mode of action of most clinical cancer immunotherapies[259]. Together with B cells, T cells form the adaptive immune system, which is characterized by cellular expansion and memory formation upon antigen encounter[260]. T cell function is intimately linked to metabolism, and therefore metabolic alterations determine T cell phenotypes. After exiting the thymus, naive T cells have a quiescent, low metabolic phenotype[261]. Within minutes after T cell receptor (TCR) activation, naive T cells upregulate their metabolic demands and switch to a glycolytic phenotype[261]. This switch is achieved by inhibition of enzymes required for mitochondrial pyruvate utilization (pyruvate dehydrogenase) and upregulation of glucose transporters such as GLUT1 (ref. 9). Co-stimulation of T cells through CD28 further promotes glycolysis through the PI3K–AKT–mechanistic target of rapamycin complex 1 (mTORC1) signalling pathway[261]. Nevertheless, T cells not only upregulate glycolysis but also augment the use of glutamine through upregulation of the glutaminase transporter and the amino acid transporters SLC28A1 and SLC28A2 (ref. 9). Multiple other transporters, including SLC7A5 for methionine and SLC16 for lactate export are upregulated upon T cell activation[261]. T cells also increase synthesis of nucleotides and ribosomes to enable cell proliferation[9].

Although the glycolytic switch is an essential early metabolic adaptation, T cells also increase mitochondrial biogenesis through the transcription factor MYC, elevating their oxygen consumption rate[9]. Importantly, mitochondria are dynamically regulated through fusion and fission throughout T cell differentiation and are required for cytolytic function[174,175].

T cells comprise cytotoxic $CD8^+$ cells and several $CD4^+$ helper T cell subsets[260]. Although central metabolic paradigms appear to be shared between these subsets, some differences have been described[9]. In addition, many tissue- and cancer-specific alterations in T cell metabolism are known[261]. For example, regulatory T cells (T_{reg} cells, an immunosuppressive $CD4^+$ T cell subset) upregulate the fatty acid receptor and the transporter CD36 to adapt to the lactate-rich tumour microenvironment[262]. After antigen-dependent priming, a small fraction of T cells become long-lived memory T cells, enabling a quicker response upon reinfection[260]. Memory T cells reprogramme their metabolic phenotype towards increased mitochondrial dependency, upregulation of fatty acid synthesis and oxidation[9]. Inhibition of glycolysis by 2-deoxyglucose or by enforcing lipid metabolism through carnitine palmitoyltransferase 1 overexpression enhances generation of $CD8^+$ T cell memory cells[9]. These effects highlight the centrality of metabolism in T cell memory formation. T cell exhaustion limits antitumour immunity owing to the enfeeblement of T cell functions upon repeated antigen exposure[263]. It leads to reduced glucose uptake and dysfunctional mitochondria, and in addition metabolic stress can cause or accelerate T cell exhaustion[263]. Importantly, T cell metabolism and function are intricately linked through epigenetic regulation[263].

Multiple hypotheses for the failure of epacadostat have been formulated, including lack of patient stratification based on IDO1 expression or immune infiltration, as well as suboptimal IDO1 inhibition due to the low dose chosen to avoid hepatotoxicity[33]. In fact, blood kynurenic acid — a potential biomarker of IDO1 inhibitor activity — was not reduced in a phase II trial of epacadostat in patients with sarcoma, supporting the idea that the inhibitor was underdosed[34]. Improved formulation strategies might offer better tumour targeting and hence ameliorate the safety profile of IDO1 inhibitors[35]. Recent work also uncovered a potential resistance mechanism to IDO1 inhibition. NAD^+ excreted by IDO1-inhibited cancer cells might spur the conversion of extracellular NAD^+ into adenosine, which inhibits T cells through A_{2A} and A_{2B} adenosine receptors[36]. Thus, combining IDO1 inhibition with adenosine receptor inhibitors (such as SCH58261 or PSB1115) improved antitumour immune responses in ovarian cancer models[36]. Of note, tryptophan depletion through IDO1 causes ribosomal frameshifting in melanoma cancer cells, resulting in immunogenic peptide presentation and immune recognition[37]. Therefore, IDO1 inhibition might inadvertently reduce the immunogenicity of cancer cells, contributing to tumour progression. Interestingly, serine deprivation similarly induces immune activation through mitochondrial dysfunction and subsequent activation of cyclic GMP–AMP synthase (cGAS) and stimulator of interferon genes (STING)[38]. Conversely, tryptophan depletion inhibits the differentiation of antitumour inflammatory dendritic cells, suggesting that IDO1 inhibitors can increase antigen presentation[39]. Hence, it remains unclear to what extent IDO1 inhibitor resistance can be explained by deficient presentation of tumour-associated antigens.

Another hypothesis that could explain IDO1 resistance builds on the compensatory effects of the other tryptophan-degrading enzymes, TDO and IDO2, on IDO1 inhibition. This would favour the development of dual IDO1–IDO2 inhibitors (for example, AT-0174) or a combination of IDO1 inhibitors with TDO inhibitors (for example, LM10)[40,41]. Moreover, AHR activity strongly correlates with the expression of L-amino oxidase IL-4-induced 1 (IL4I1), more so than with expression of IDO1 and TDO[42]. IL4I1 converts tryptophan into indole-3-aldehyde (I3A) and indole-3-pyruvic acid (I3P), which both activate AHR even in the context of IDO1 inhibition[42]. IL4I1 is an exciting new player in tryptophan metabolism, implicated in immunosuppression via immature B cells[43], tumour-associated macrophages[44] and inhibition of ferroptotic cell death in cancer cells[45]. It can be speculated, yet remains to be demonstrated, that a systematic investigation of potential resistance mechanisms, more sophisticated dose-finding studies and optimized formulations, as well as careful patient stratification, might have avoided the fiasco of the phase III trials aborting the clinical development of IDO1 inhibitors.

Indoximod (D-1-methyl-tryptophan) acts on the tryptophan pathway, although not by directly inhibiting IDO1 but by relieving the detrimental effects of tryptophan depletion on mechanistic target of rapamycin (mTOR) signalling in immune cells. Indoximod has been tested in several phase I and II trials, was found to be safe and showed early signs of efficacy in melanoma, adult and paediatric brain cancer, and prostate cancer, although it failed to show benefits in breast cancer[46,47]. The clinical development of indoximod is now focused on paediatric brain cancer (NCT04049669, NCT05106296). Another agent, a pegylated kynureninase, targets kynurenine to improve tumour lymphocyte infiltration and thereby the efficacy of checkpoint inhibition in murine syngeneic models[48]. Thus, ongoing preclinical and clinical research should lead to further agents that target the tryptophan–kynurenic axis.

Glutamine and α-ketoglutarate

Unlike tryptophan, glutamine is not an essential amino acid. Nonetheless, glutamine metabolism fuels and regulates cancer cell proliferation[6,49]. Cancer cells have a high demand for glutamine, in part owing to the upregulation of glutamine transporters driven by *MYC* gene amplification[50,51]. In cells, glutamine is converted into glutamate by glutaminase, then metabolized to α-ketoglutarate (αKG) to fuel the tricarboxylic acid (TCA) cycle (also called the citric acid cycle) in mitochondria[49] (Fig. 1). The process of αKG fuelling the TCA cycle (anaplerosis) enables the removal of other metabolites from this cycle (cataplerosis) that can then be used for anabolic reactions. These metabolites include citrate, which generates fatty acids via reductive carboxylation[49]. Glutamine is also necessary to counteract reactive oxygen species (ROS) through glutathione synthesis[52]. Interestingly, αKG

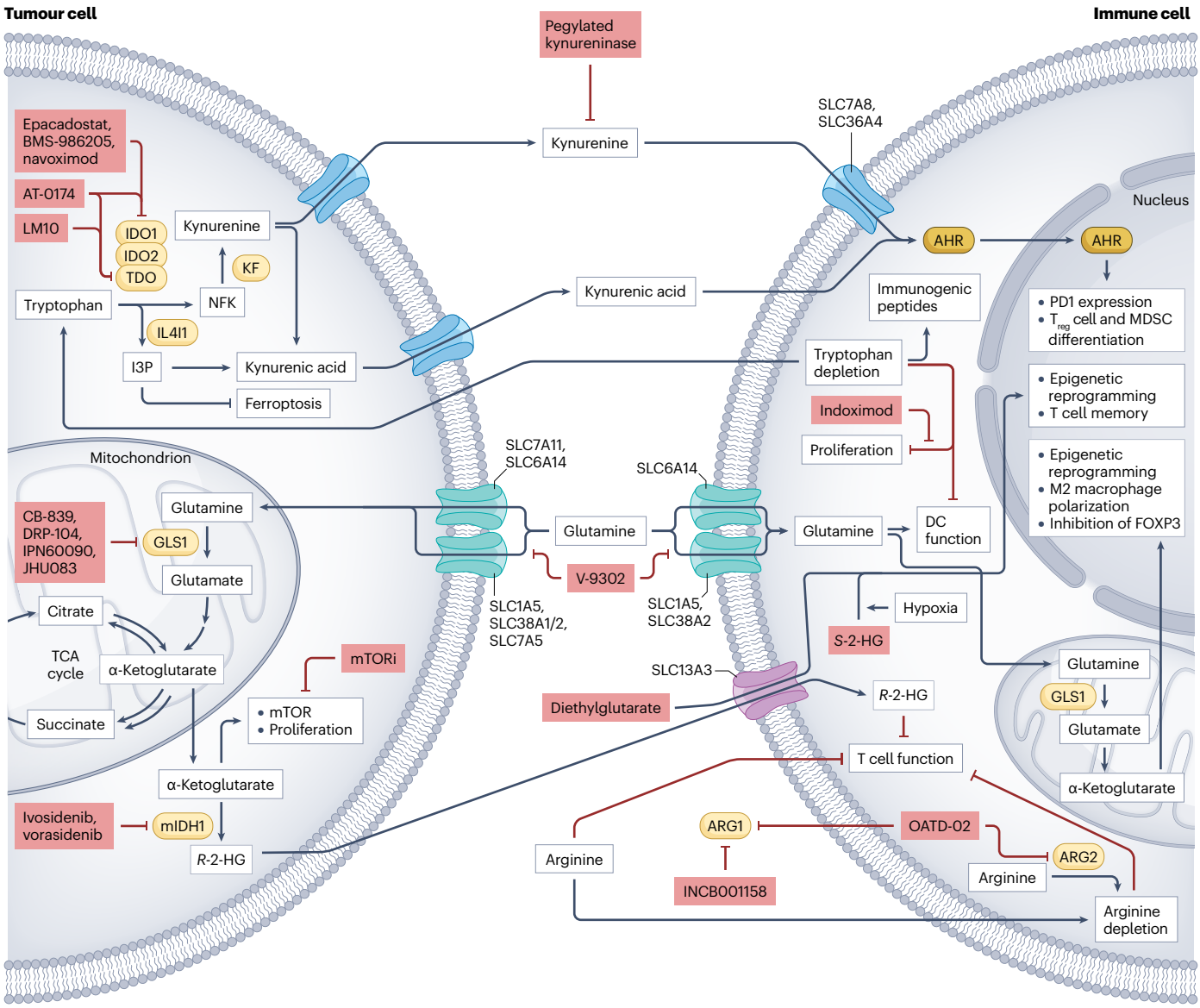

Fig. 1 | Targeting amino acid metabolism to improve cancer immunotherapy. The pathways involved in amino acid metabolism in tumour cells (left) and immune cells (right). Tumour cells use a series of enzymes to metabolize tryptophan into kynurenic acid, which activates the aryl hydrocarbon receptor (AHR) to promote immune suppression. Tumour cells also consume large amounts of glutamine to fuel their tricarboxylic acid (TCA) cycle, so glutamine transporters are an opportunity for intervention. The glutamine derivative α-ketoglutarate has multiple effects that promote proliferation of tumour cells and also impacts epigenetic modulation in myeloid and T cells. α-Ketoglutarate is also metabolized into *R*(−)-2-hydroxyglutarate (*R*-2-HG) by mutated isocitrate dehydrogenase 1 (mIDH1), dampening T cell function. Arginine depletion in the tumour microenvironment has detrimental effects on T cell function and can be counteracted by inhibitors of ARG1 arginase. Therapeutic interventions are highlighted in red boxes. DC, dendritic cell; GAD1, glutamate decarboxylase 1; GLS1, glutaminase 1; IDO, indoleamine oxidase; I3P, indole-3-pyruvic acid; IL4I1, IL-4-induced 1; KF, kynurenine formamidase; MDSC, myeloid-derived suppressor cell; mTORi, mechanistic target of rapamycin inhibitor; NFK, *N*-formylkynurenine; TDO, trpytophan-2,3-dioxygenase; TPH1, tryptophan 5-hydroxylase 1; T_{reg} cell, regulatory T cell.

Table 1 | Selected clinical trials of metabolites and metabolic interventions

Drug	Target	Indication	Combination	Trial ID; phase	Result and/or status	Ref.
Ivosidenib	mIDH1	mIDH1-AML	Azacitidine	NCT03173248; III	Significant benefit on PFS	87
Vorasidenib	mIDH1, mIDH2	Grade 2 IDH-mutant glioma	None	NCT04164901; III	Significant benefit on PFS	88
Vorasidenib	mIDH1, mIDH3	Recurrent or progressive mIDH1 glioma	Pembrolizumab	NCT05484622; I	Recruiting	–
Oleclumab (MEDI9447)	CD73	Unresectable stage III NSCLC	Durvalumab, chemo-irradiation	NCT05221840; III	Recruiting	–
IPH5201	CD39	Resectable NSCLC	Durvalumab, chemotherapy; neoadjuvant and adjuvant	NCT05742607; II	Recruiting	–
TTX-030	CD39	Metastatic pancreatic adenocarcinoma	Chemotherapy with or without budigalimab	NCT06119217; II	Active, not recruiting	–
IPH5201	CD39	Resectable NSCLC	Durvalumab, chemotherapy; neoadjuvant and adjuvant	NCT05742607; II	Recruiting	–
Indoximod	mTOR, tryptophan depletion	Paediatric patients with progressive primary malignant brain tumours	Temozolomide	NCT02502708; II	Well tolerated, favourable response rate	257
Indoximod	mTOR, tryptophan depletion	Refractory metastatic prostate cancer	Sipuleucel-T	NCT01560923; II	Well tolerated, significant clinical improvement	258
Indoximod	mTOR, tryptophan depletion	Relapsed brain tumours or newly diagnosed DIPG	Chemotherapy and radiation	NCT04049669; II	Recruiting	–
Indoximod	mTOR, tryptophan depletion	Paediatric brain cancer	Ibrutinib and chemotherapy	NCT05106296; I	Recruiting	–
AT-0174	IDO1, TDO	Advanced solid tumours	None	ACTRN12623000956606; I	Recruiting	–
CB-839 (telaglenastat)	Glutaminase	Advanced or metastatic RCC	Everolimus	NCT03163667; II	Well tolerated, improved PFS	71
CB-839 (telaglenastat)	Glutaminase	Advanced-stage NSCLC	Sapanisertib	NCT04250545; I	Active, not recruiting	–
IPN60091	Glutaminase	Advanced solid tumours	Bevacizumab and paclitaxel	NCT05039801; I	Recruiting	–
OATD-02	Arginase 1, arginase 2	Advanced or metastatic solid tumours	None	NCT05759923; I	Recruiting	–
Etrumadenant (AB928)	AA_2R	Metastatic colorectal cancer	Combinations of zimberelimab, mFOLFOX-6, bevacizumab	NCT04660812; I, II	Manageable toxicity profile and improvements in PFS and OS	130
Ciforadenant	AA_2R	First-line advanced RCC	Ipilimumab and nivolumab	NCT05501054; I, II	Recruiting	–
High-fibre diet	Gut microbiota modulation	Metastatic or unresectable stage III–IV melanoma	Pembrolizumab or nivolumab	NCT04645680; II	Active, not recruiting	215
Camu-camu berry powder	Gut microbiota modulation	Advanced NSCLC and melanoma	Standard-of-care ICB (pembrolizumab, nivolumab and/or ipilimumab)	NCT05303493; I	Recruiting	–
Fluoxetine	Serotonin transporter	Colorectal cancer	Neoadjuvant	NCT06225011; I	Not yet recruiting	–

A list of all clinical trials discussed in this Review can be found in the Supplementary information. AA_2R, adenosine A_2 receptor; AML, acute myeloid leukaemia; DIPG, diffuse intrinsic pontine glioma; ICB, immune checkpoint blockade; IDO1, indoleamine 2,3-dioxygenase 1; mIDH1, mutant isocitrate dehydrogenase 1; mTOR, mechanistic target of rapamycin; NSCLC, non-small-cell lung cancer; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; TDO, trpytophan-2,3-dioxygenase.

increases fatty acid oxidation and promotes the development of immunosuppressive M2 macrophages through epigenetic reprogramming[53]. In contrast, αKG was recently linked to programmed cell death 1 ligand 1 (PDL1) expression and responsiveness to anti-PD1 therapy[54]. Glutamine deprivation favours T_{reg} cell differentiation, whereas αKG can inhibit T_{reg} cell differentiation, reduce expression of the T_{reg} cell transcription factor FOXP3, and promote a pro-inflammatory phenotype in T cells[55,56]. The contrasting effects of αKG on T cells and macrophages highlight that studying metabolic interventions on isolated cell types cannot predict their net effect on antitumour immunity.

Given the importance of glutamine in cancer cell proliferation, targeting glutaminase is an intensely studied treatment strategy[57]. Glutaminase inhibition disrupts the glutamate metabolic pathway, leading to decreased production of crucial metabolites necessary for biosynthesis and redox balance, ultimately impairing tumour growth and viability[58]. For example, inhibition of glutaminase by 6-diazo-5-oxo-l-norleucine (DON) or its pro-drug JHU083 leads to tumour regression, improved T cell function[59] and dampening of MDSCs[60] (Fig. 1). Similarly, DON shows positive effects during ex vivo chimeric antigen receptor (CAR)-T cell production by increasing the fraction of central memory cells[61].

The pro-drug JHU083 requires enzymatic cleavage in the TME, which limits the gastrointestinal toxicity observed for DON, and JHU083 synergizes with ICB in mouse models[59,62]. However, no clinical trials with JHU083 have been registered yet. DRP-104 (sirpiglenastat) is another DON pro-drug that was tested in a phase I clinical trial on patients with advanced solid tumours, but no results have been reported (NCT04471415). DRP-104 is now being evaluated in patients with fibrolamellar carcinoma refractory to anti-PDL1 (ref. 63). IPN60090 is a structurally unrelated oral glutaminase 1 (GLS1) inhibitor that showed a good safety profile with relevant reduction of glutamate to glutamine ratios in peripheral blood mononuclear cells (PBMCs)[64]. IPN60090 is being tested in a phase I trial in combination with bevacizumab and paclitaxel in advanced solid tumours (NCT05039801).

CB-839 (telaglenastat) is the most advanced glutaminase inhibitor in clinical development. CB-839 improved antitumour immunity in co-cultures and immunocompetent melanoma models when combined with immune checkpoint inhibitors[65]. This was attributed to a more potent inhibition of αKG production in tumour cells than in T lymphocytes. In immunocompetent mice bearing *KRAS*-mutant lung cancers, glutaminase is locally upregulated in tumours, but the combination of CB-839 with PD1 checkpoint blockade impaired T cell activation and clonal expansion[66]. Therefore, depriving tumour cells of glutamine must be carefully balanced with the potential negative impact of glutaminase inhibition on immune cells. Moreover, glutamine dependency of mouse tumours can vary greatly in vitro and in vivo[67]. CB-839 did not improve progression-free survival of patients with metastatic clear-cell RCC when combined with the VEGFR2/MET/AXL inhibitor cabozantinib[68]. Unfortunately, in this trial, glutaminase activity was not assessed by measuring plasma glutamine levels. Another trial investigating CB-839 in combination with nivolumab in melanoma, clear-cell RCC and NSCLC was terminated for lack of efficacy (NCT02771626). The loss of *KEAP1* that occurs in ~20% of lung cancers increases the activity of the oxidative stress-responsive transcription factor NRF2, which leads to dependency of cancer cells on glutaminolysis[69]. However, a clinical trial evaluating the combination of PDL1 blockade and CB-839 in a selected cohort of patients with *KEAP1*- or *NRF2*-mutated NSCLC was terminated for lack of efficacy (NCT04265534), shedding doubts on the glutamine dependency of these patients with NSCLC.

Glutaminolysis and mTOR activation are intricately linked, because the amino acid leucine activates glutamate dehydrogenase, which promotes the αKG-mediated activation of mTOR[70] (Fig. 1). This connection offers another strategy to target the TME. Accordingly, a randomized double-blinded phase II trial enrolling patients with advanced RCC showed that CB-839 was well tolerated in combination with the mTOR inhibitor everolimus and improved progression-free survival[71]. CB-839 is also being investigated in combination with another mTOR inhibitor (sapanisertib) in advanced-stage NSCLC (NCT04250545). In this trial, metabolic response to CB-839 will be measured using glutamine and deoxyglucose-based positron emission tomography (PET) tracers. Using metabolite-based PET tracers to quantify target inhibition, as well as immune activation, is an exciting new perspective for various immunotherapy interventions[72]. In summary, although many glutaminase inhibitors have been developed, no clinical efficacy in combination with ICB has been observed. However, rigorous patient selection and new combination regimens have the potential to offer clinically effective therapeutic approaches.

Targeting glutamine transporters, including SLC7A11, SLC1A5, SLC6A14 and SLC38A1/2, constitutes another option to deplete glutamine from tumour cells[57] (Fig. 1). Because amino acid metabolism affects the susceptibility of cells to ferroptosis, inhibition of glutamine transporters sensitizes cells to the induction of ferroptosis[73]. However, inhibition of glutamine transporters can also compromise the proliferation and differentiation of T cells, which rely on glutaminolysis, and thereby could impair antitumour immunity[74]. Similarly, deletion of SLC38A2 impairs the function of conventional type 1 dendritic cells and antitumour immunity in vivo[75]. However, V-9302, a small molecule inhibitor of SLC1A5, reduced tumour growth while it decreased T cell infiltration and favoured M2 macrophage polarization in the MC38 syngeneic colorectal cancer (CRC) model[57,76]. Similarly, V-9302 had potent antitumour effects in mouse models of triple-negative breast cancer, in which it improved the effector functions of $CD4^+$ T cells and granzyme B^+ $CD8^+$ T cells[77]. In an in vitro study, the application of V-9302 increased T cell memory differentiation and maintained glutathione synthesis. This effect was attributed to the upregulation of SLC6A14 specifically on T cells, which compensated for the adverse effects of V-9302 in glutamine deprivation through SLC1A5 inhibition[77]. However, the specificity of V-9302 is controversial, as one study found no evidence for its claimed SLC1A5 specificity but demonstrated inhibition of SLC7A5 and SLC38A2 (ref. 78). Developing truly specific inhibitors for the various glutamine transporters and increasing their potency are likely to be necessary for future clinical applications.

Glutarate

Isocitrate dehydrogenase 1 (IDH1), IDH2 and IDH3 fulfil essential roles in the TCA cycle, lipogenesis and other metabolic processes[79]. Mutations in the gene encoding IDH1 occur in a large subset of human gliomas termed astrocytomas or oligodendrogliomas, as well as in acute myeloid leukaemia (AML), chondrosarcomas and cholangiocarcinomas[80]. These mutations lead to aberrant production of the oncometabolite *R*(−)-2-hydroxyglutarate (*R*-2-HG) from αKG[81] (Fig. 1). Tumour-derived *R*-2-HG enters T cells through the transporter SLC13A3, where it inhibits lactate dehydrogenase (LDH), impairs signalling by nuclear factor of activated T cells (NFAT) and leads to reduced cytotoxicity and interferon-γ (IFNγ) secretion[82,83]. *R*-2-HG also inhibits several proteins involved in histone demethylation and promotes lactate secretion by dendritic cells and AML cells[84]. Overall, *R*-2-HG suppresses T cells and thereby antitumour immunity.

In light of the immunosuppressive effects of *R*-2-HG, multiple IDH1 inhibitors have been developed. An orally administered IDH1 inhibitor BAY1436032, which is specific for mutant IDH1 (mIDH1), synergized with PD1 blockade in a murine syngeneic tumour model[83]. Similarly, mIDH1 inhibition rescued T cell function and synergized with CTLA4 blockade in a mouse model of cholangiocarcinoma[85]. IDH1 inhibitors then moved into the clinic, and the FDA approved the first mIDH1 inhibitor, ivosidenib, for the treatment of mIDH1-AML[86,87] (Fig. 1). Combinations of mIDH1 inhibitors and immune checkpoint blocking antibodies are being clinically tested in patients with cholangiocarcinoma (NCT05921760). Furthermore, in a phase III study, the brain-penetrating IDH1 and IDH2 inhibitor vorasidenib improved progression-free survival in patients with mIDH1 grade 2 glioma[88]. Given these encouraging clinical results and the known immunosuppressive effects of *R*-2-HG, vorasidenib is now being tested in combination with pembrolizumab in patients with recurrent or progressing mIDH1 glioma in a phase I clinical trial (NCT05484622). In murine glioma models, mIDH1 inhibition synergized with irradiation, temozolomide and PDL1 blockade[89].

Elevated levels of *R*-2-HG in mIDH1 tumours were shown to increase kynurenine production, pointing to major crosstalk between two important immunosuppressive pathways[90]. In mice, mutation of IDH1

inhibited myeloid differentiation, which could be relieved by pharmacological AHR inhibition[90]. These results suggest that patients with mIDH1 tumours might profit from AHR blockade.

Interestingly, in hypoxic conditions, activated T cells produce up to millimolar intracellular concentrations of the *R*-2-HG enantiomer *S*(+)-2-HG[91] (Fig. 1). This enantiomer suppresses T cell effector functions and proliferation in vitro, while preserving T cell memory features through effects on histone and DNA demethylation and HIF1α stability[91]. Exposure of antigen-specific T cells to *S*-2-HG in vitro improved their persistence upon adoptive transfer into mice and boosted their antitumour effects against lymphomas[91].

A glutarate derivative diethyl glutarate (DEG) was shown to preserve T cell memory markers without adverse effects on cell proliferation and to boost antitumour immunity in murine tumour models[92] (Fig. 1). DEG competitively inhibits several epigenetic enzymes that require αKG and alters T cell metabolism by glutarylation of PDH E2 subunit[92].

Altogether, these findings indicate how glutarate and its derivatives shape T cell differentiation and could be used for immunotherapy.

Arginine

Arginine is a semi-essential proteinogenic amino acid that serves as a precursor for many metabolites, including citrulline, creatine, glutamate, ornithine and urea[93]. In tumours, arginine is metabolized to polyamines by arginase 1 (ARG1) expressed by immunosuppressive macrophage subsets (M2) and MDSCs[94] (Fig. 1). The depletion of arginine from the TME inhibits T cell function[95] (Fig. 1). MDSCs express nitric oxide synthase (NOS), which converts arginine into nitric oxide, which has immunosuppressive effects[96]. Accordingly, oral arginine supplementation enhances antitumour immunity in murine models by suppressing MDSCs[97]. The oral arginase inhibitor INCB001158 (numidargistat) was recently administered to patients with advanced solid tumours in a phase I trial[98]. As a monotherapy, INCB001158 was tolerated and induced a dose-dependent increase in plasma arginine levels, but failed to affect infiltration of T cells into tumours. INCB001158 was also tested with anti-PD1 antibodies in patients with solid tumours[99]. No dose-limiting toxicities were reached, but no activity was observed. In an attempt to generate better arginase inhibitors, the compound OATD-02 was designed to have a longer half-life, and to inhibit both extracellular ARG1 and intracellular ARG2 (ref. 100) (Fig. 1). OATD-02 was effective in murine tumour models and is being investigated in a first-in-human trial in patients with advanced and metastatic cancer (NCT05759923)[100]. This clinical study will be crucial to give a first indication of whether dual ARG1 and ARG2 targeting is more effective than ARG1 targeting with INCB001158.

Non-proteinogenic amino acids and amino acid derivatives

A wide range of non-proteinogenic amino acids are produced endogenously and have effects on immune cells. For example, the non-proteinogenic amino acid taurine augments T cell proliferation in aged mice[101] and modulates cell death induced by T cell activation[102,103]. Taurine also boosted OXPHOS in T cells and improved antitumour responses in mouse models of PD1 blockade[104]. Intriguingly, cancer cells outcompete T cells for taurine consumption by upregulating the taurine transporter SLC6A6. The depletion of taurine leads to T cell exhaustion owing to the activation of transcription factors STAT3 and ATF4 (ref. 105).

Amino acids can be intermediaries for molecules with potent signalling effects, such as neurotransmitters. The neurotransmitter γ-aminobutyric acid (GABA) is an extracellular signalling molecule in the brain and in pancreatic islets. Cancer cells with aberrant overexpression of glutamate decarboxylase 1 (GAD1) rewire glutamine metabolism to synthesize GABA outside the nervous system[106]. GABA activates the metabotropic $GABA_B$ receptor ($GABA_BR$), resulting in inhibition of glycogen synthase kinase 3β (GSK3β) activity, enhanced β-catenin signalling and tumour cell proliferation as well as suppression of tumour-infiltrating $CD8^+$ T cells. Targeting GAD1 or $GABA_B$ in mouse tumour models overcomes resistance to PD1 blockade[106] and in patients, increased intratumoural GABA levels predict poor prognosis[106]. B cell-specific inactivation of the GABA-generating enzyme GAD67 enhanced antitumour response[107]. Altogether, these findings suggest an immunosuppressive role for GABA in the TME. Intriguingly, the $GABA_BR$ antagonist 2-OH-saclofen and the GAD1 inhibitor 3-mercaptopropionate (3-MPA) synergized with PD1 blockade in syngeneic murine tumour models[106]. Similarly, neutralization of acyl-CoA binding protein, which serves as an endogenous allosteric activator of $GABA_AR$, synergized with PD1-targeting immunotherapy or chemoimmunotherapy, offering a new potential treatment strategy[108].

Serotonin (5-hydroxytryptamine) is a neurotransmitter produced from tryptophan with pro-tumourigenic and pro-inflammatory effects[109]. Peripheral serotonin is primarily produced by tryptophan 5-hydroxylase 1 (TPH1) in enterochromaffin gut cells, then taken up by platelets and released at sites of coagulation[110]. Intriguingly, intratumoural serotonin levels negatively correlate with $CD8^+$ T cell infiltration, and serotonin leads to increased PDL1 expression through protein serotonylation[111]. Oral treatment with fluoxetine, which blocks serotonin transporter (SERT)-mediated serotonin uptake into platelets, reduced tumour growth in syngeneic models[111]. Also, fluoxetine and the clinically approved TPH1 inhibitor telotristat-ethyl reduced serum serotonin and synergized with PD1 blockade in murine tumour models[111]. However, concluding that the anticancer effects of fluoxetine are mediated by SERT inhibition might be premature because fluoxetine is also reported to inhibit sphingomyelin metabolism and epidermal growth factor receptor signalling[112]. In a planned clinical trial, fluoxetine will be applied daily for 10 days before surgery to patients with CRC to investigate whether it modifies immune cell composition (NCT06225011).

Nucleosides: adenosine

Beyond their role as building blocks of DNA and RNA, nucleosides have essential functions in energy storage and signalling, as exemplified for extracellular ATP. Under conditions of injury, ischaemia or cell death, cellular ATP is released into the extracellular space and can act as an activator of the NLRP3 inflammasome, promoting tumour cell survival and metastasis through activation of the P2X and P2Y purinoceptors (P2XR and P2YR)[113]. ATP accumulates in tumours, but is rapidly degraded into adenosine by the membrane-bound ectonucleotidases CD39 and CD73 (NT5E), which are expressed by tumour and immune cells[113,114] (Fig. 2). Alternatively, adenosine is generated when NAD^+ is converted into AMP by CD38 and CD203a, and AMP is then transformed into adenosine by CD73 (ref. 115). Adenosine acts on four G protein-coupled receptors A_1, A_{2A}, A_{2B} and A_3 (ref. 11). Adenosine increases tumour cell proliferation, metastasis and angiogenesis through the A_{2A} and A_{2B} receptors, which are expressed on tumour cells, endothelial cells and pericytes[114] (Fig. 2). In addition, adenosine supports polarization of immunosuppressive M2 macrophages and promotes T_{reg} cell differentiation[114] (Fig. 2). Adenosine also directly inhibits the proliferation, activation and cytokine release of effector T and natural killer (NK) cells[114]. Expression of the

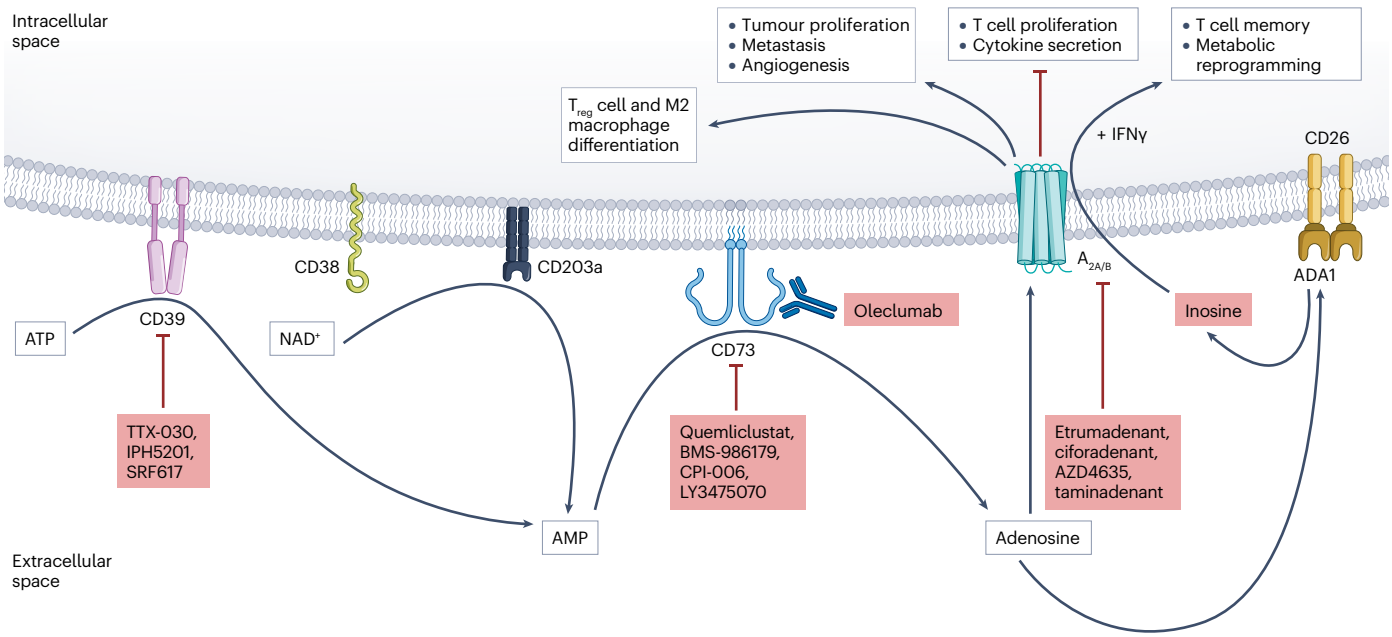

Fig. 2 | Targeting nucleoside metabolism in antitumour immunity. Nucleoside metabolism is regulated in both tumour and immune cells through transmembrane receptors. Initially, the receptor CD39 metabolizes ATP into AMP. In addition, AMP can be generated from NAD^+ by CD38 and CD203a. The receptor CD73 then converts AMP into adenosine, which impairs antitumour immunity through binding of A_{2A} and A_{2B} adenosine receptors on myeloid and T cells. Inhibitors of CD39, CD73 or A_{2A} and A_{2B} aim to prevent these suppressive effects. Adenosine can also be converted into inosine through the adenosine deaminase ADA1 (bound to CD26), which promotes T cell memory formation. Therapeutic interventions are highlighted in red boxes. IFNγ, interferon-γ; T_{reg} cell, regulatory T cell.

A_{2A} and A_{2B} receptors is required for adenosine-mediated immunosuppression of tumours, and A_{2A} and A_{2B} inhibitors such as caffeine can improve tumour rejection[116]. Similarly, CD73 knockout mice also show enhanced immune-mediated inhibition of tumour growth and reduced metastasis[117]. These and many similar findings have encouraged the development of inhibitors of the adenosine pathway to overcome immunosuppression mechanisms.

The adenosine pathway can be targeted by inhibiting the generation of adenosine by CD39 and CD73 or by blocking the A_{2A} and A_{2B} receptors (Fig. 2). The clinically most advanced anti-CD73 agent is the monoclonal antibody oleclumab (MEDI9447). Oleclumab enhances the antitumour effects of both myeloid and lymphoid cells in syngeneic murine tumour models and synergizes with PD1 blockade[118]. In clinical trials, oleclumab showed a manageable safety profile and in combination with PDL1 blockade it improved progression-free survival in patients with unresectable stage III NSCLC (the COAST clinical trial)[119,120]. On the basis of these promising results, oleclumab is now in a phase III trial (NCT05221840). Another CD73 inhibitor is the small molecule quemliclustat (AB680). It showed potent effects in vitro and in murine syngeneic tumour models[121]. In the ARC-8 phase Ib trial in patients with treatment-naive metastatic pancreatic adenocarcinoma, quemliclustat combined with anti-PD1 antibodies and standard chemotherapy was safe and showed promising overall survival data[122]. Quemliclustat is being tested in multiple phase II trials, mostly together with anti-PD1 antibodies. It is also being combined with the A_{2A}–A_{2B} antagonist etrumadenant plus anti-PD1 antibodies (NCT04381832). Other CD73 inhibitors, such as BMS-986179, CPI-006 and LY3475070, showed manageable safety profiles in early-stage clinical trials and are undergoing further clinical testing[123,124].

By comparison with CD73 inhibition, inhibition of CD39 has the additional benefit of resulting in the extracellular accumulation of ATP, which potentiates antitumour immunity through activation of dendritic cells and macrophages[125,126]. Although no clinical-stage small molecule inhibitors are available, several antibodies targeting CD39 have progressed to clinical trials (Fig. 2). In the first trials, the CD39 antibodies SRF617 and IPH5201 were well tolerated at doses that inhibited CD39 in the tumour[127,128], although another trial using SRF617 was terminated (NCT05177770). IPH5201 is now being evaluated in combination with anti-PD1 blockade in a phase II trial in NSCLC (NCT05742607). Moreover, the CD39 antibody TTX-030 is being tested in combination with an anti-PD1 antibody and chemotherapy in patients with metastatic pancreatic cancer (NCT06119217)[129]. These trials are essential to assess the benefit of CD39 blockade compared with, or potentially in combination with, CD73 or A_{2A}–A_{2B} inhibitors[126].

Downstream of CD39 and CD73, multiple A_{2A} and A_{2B} adenosine receptor inhibitors have been clinically tested. The orally available selective A_{2A}–A_{2B} inhibitor etrumadenant (AB928) was evaluated in a phase Ib/II trial (ARC-9) in combination with PD1 blockade, the anti-VEGF antibody bevacizumab and the FOLFOX chemotherapy regime[130] in patients with metastatic colorectal cancer (mCRC). A preliminary report indicates that etrumadenant has a manageable toxicity profile and leads to improvements in survival of patients with mCRC compared with the third-line standard of care, the multi-kinase inhibitor regorafenib[130]. Etrumadenant is being further tested in multiple

phase II trials, especially in combination with PD1 blockade. Similarly, the A_2-antagonist ciforadenant was safe and showed signs of efficacy as a monotherapy in patients with refractory RCC[131]. On-target activity of ciforadenant was confirmed in PBMCs from patients, and it caused increased T cell infiltration and downregulation of an adenosine-related gene expression signature in tumour biopsy samples. Based on preclinical evidence of its synergy with checkpoint inhibitors, ciforadenant is being investigated in combination with anti-PD1 and anti-CTLA4 antibodies in a phase I/IIa trial in patients with advanced RCC[132]. Other A_{2A} and A_{2B} inhibitors have shown only low response rates in early-stage clinical trials, which have been terminated[133]. For example, AZD4635 was tested in combination with anti-PD1 and docetaxel (chemotherapy)[134], and taminadenant (NIR178)[135] was tested in combination with anti-PD1 antibody or the CD73 inhibitor NZV930 (NCT03207867, NCT03549000). We believe that pre-treatment evaluation of adenosine pathway activity (including CD73 and CD39 expression) in the tumour and an assessment of on-target activity are key to the future development of adenosine pathway inhibitors.

Given the immunosuppressive effects of adenosine on T cells, adenosine pathway inhibition has also been explored to improve the efficacy of CAR-T cells. Inhibition of A_{2A} and/or A_{2B} by etrumadenant was shown to enhance the efficacy of CAR-T cells in a mouse model of colon cancer[136]. Another preclinical study found that overexpression of adenosine deaminase, which causes degradation of adenosine to inosine, improved CAR-T cell function more than CD39, CD73 or A_2 knockout[137]. The authors linked this to the effects of inosine, which enhances in vitro expansion and efficacy of CAR-T cells through metabolic and epigenetic reprogramming (Fig. 2). Intriguingly, inosine might be produced by intestinal bacteria, the abundance of which is associated with ICB responses[138]. Oral inosine supplementation to mice improved their ICB response, which depended upon the expression of the A_{2A} and A_{2B} receptors by T cells and IFNγ[138] (Fig. 2). Another study showed that an injectable pegylated form of recombinant adenosine deaminase was efficacious in syngeneic mouse tumour models and showed synergy with PD1 blockade[139]. These results should encourage additional efforts to therapeutically target adenosine-mediated immunosuppression.

Glycolysis and oxidative phosphorylation

Glycolysis

Glycolysis is a multistep process that converts glucose into pyruvate (Fig. 3) and generates two molecules of ATP per glucose molecule. It fuels OXPHOS by mitochondria and provides essential building blocks for the biosynthesis of nucleotides and amino acids[140]. Increased glucose uptake is a hallmark of tumour cells and is exploited to image tumours by [^{18}F]fluorodeoxyglucose PET[141]. The amplified glucose utilization by malignant cells can lead to glucose deprivation in the TME[142]. This, in turn, leads to a lack of the glucose metabolite phosphoenolpyruvate (PEP) in T cells, which compromises its role in sustaining Ca^{2+}–NFAT signalling[142]. Boosting PEP production by overexpressing phosphoenolpyruvate carboxykinase 1 (PCK1) enhances T cell effector functions and restricts cancer progression (Fig. 3). Similarly, deficiency in the GLUT1 glucose transporter restrains differentiation of effector T cells but does not affect expansion of T_{reg} cells, which are important immunosuppressive cells in the TME[143]. Another study confirmed that T cells and cancer cells compete for glucose within the TME and blockade of PDL1 signalling reduces mTOR activity and glucose utilization by tumour cells[144]. However, it has also been reported that glucose metabolism in T cells is restrained by a lack of glutamine rather than glucose in the TME[76]. Interestingly, in syngeneic mouse colorectal tumours, myeloid cells have a major role in glucose uptake[76]. In this model, the glutamine transport inhibitor V-9302 reduced tumour mass, albeit at the expense of decreased T cell infiltration and M2 macrophage polarization[76].

Given the highly glycolytic phenotype of tumour cells, inhibition of glycolysis with the hexokinase inhibitor 2-deoxyglucose (2-DG) has been tested in clinical trials in combination with chemotherapies, although with limited success[145]. Inhibitors of the glucose transporters GLUT1–4 have also been developed. These inhibitors reduce tumour growth in vitro and in immunocompromised murine models[146]. Importantly, however, GLUT1 and GLUT2 inhibitors and 2-DG inhibit the activation of T cells, again exemplifying how targeting tumour metabolism can restrict immune cell activity. Therefore, these inhibitors are now being evaluated for their use in autoimmune diseases instead of in cancer[143,147,148]. By contrast, in cultures of expanding CAR-T cells, glucose restriction or glycolysis inhibition enriches memory T cells, preserves effector functions and reduces exhaustion[149,150]. Similar effects on CAR-T cells were shown for inhibitors of the PI3K–AKT–mTOR signalling pathway (which connects cell proliferation with metabolism), underscoring the complex interplay between metabolism, growth and T cell differentiation[151–154]. Modulation of metabolism during ex vivo expansion of cell therapy products provides an exciting new opportunity for the in vitro use of metabolic modulators that are too toxic to be used in vivo.

Lactate

In 1925, Otto Warburg described that, in contrast to normal cells, cancer cells accumulate lactate even when cultured in normoxic conditions. This 'Warburg effect', has been widely confirmed across diseases, models and patients[7,155]. High levels of lactate are produced by tumour cells through exacerbated aerobic glycolysis and also from glutaminolysis via TCA cycle intermediates[156]. Activated T cells similarly have increased aerobic glycolysis and lactate production, which are essential for IFNγ production[157]. Beyond the harmful effects of lactic acid-induced acidosis, elevated levels of pH-neutral lactate can dampen cytotoxic T and NK cell effector functions through downregulation of NFAT and reduced expression of crucial effector proteins such as IFNγ[158,159] (Fig. 3). T_{reg} cells tolerate high lactate levels and actually use it as an energy source within the TME[160,161]. Gu et al.[162] reported that lactylation of the membrane-organizing extension spike protein (MOESIN) drives TGFβ signalling, stabilizes the T_{reg} cell transcription factor FOXP3 and favours T_{reg} cell accumulation in the TME. The accumulation of lactate in diverse cancers and its adverse effects on local immune cells have motivated researchers to devise numerous strategies to interfere with this pathway.

Lactate is produced through LDHA, for which several inhibitors have been developed. For example, the LDHA inhibitor GSK2837808A synergized with adoptive cell therapy in a murine tumour model[163]. However, because of their inherent toxicity, LDHA inhibitors have not been clinically developed. Inhibition of lactate export from cells by monocarboxylate transporters (MCTs) 1 and 4 could provide an alternative to LDHA inhibitors. Thus, the MCT1 inhibitor AZD3965 mediated anticancer effects in immunocompromised mice[164] and progressed to a phase I trial in advanced solid tumours and lymphomas[165]. It showed dose-limiting toxicities affecting the retina, and one case of acidosis, as well as one case of increased cardiac troponin I, were reported[165]. A tolerated daily dose that caused MCT1 inhibition was identified[165] but no further clinical investigation followed. However, the findings

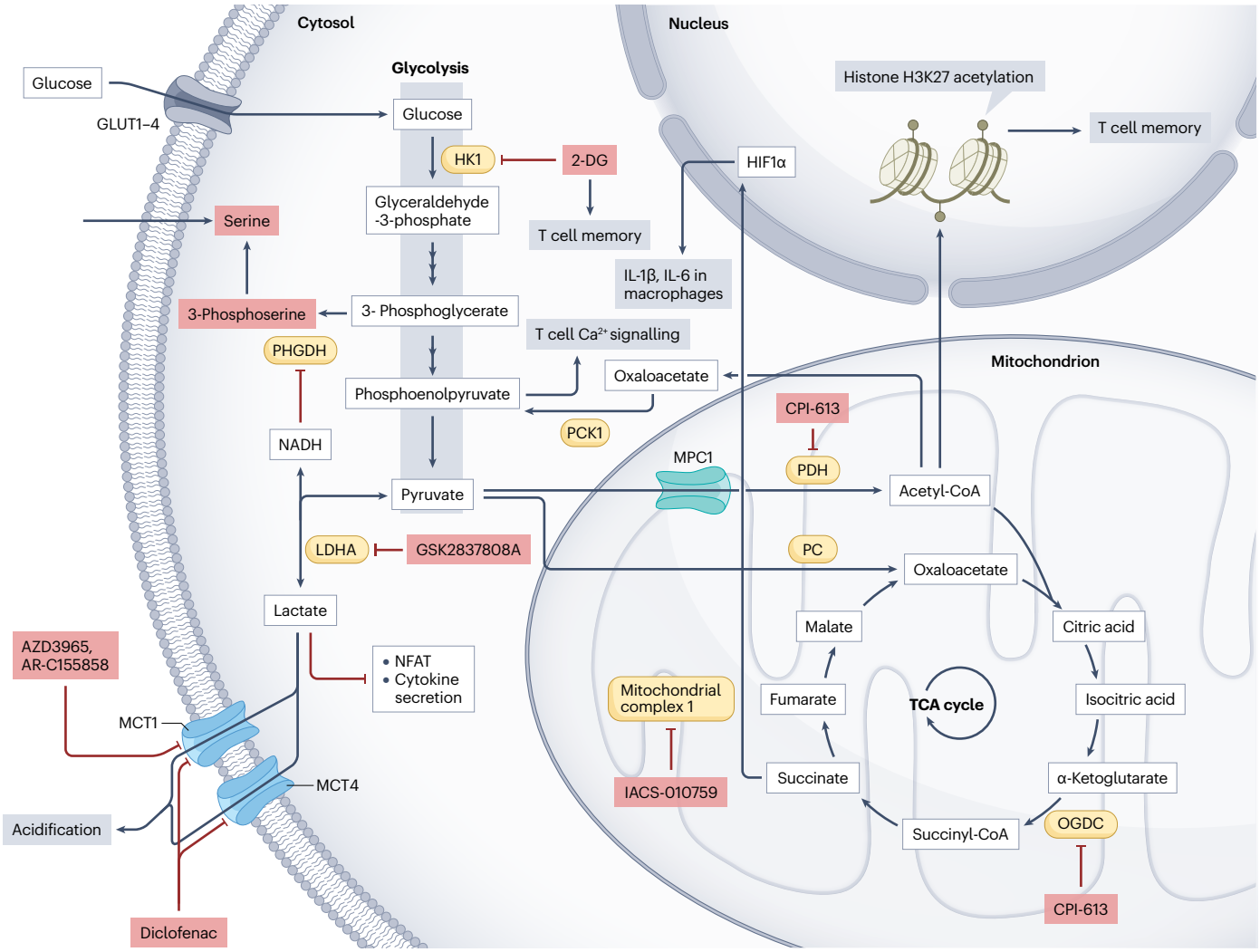

Fig. 3 | Metabolic interventions in glycolysis and mitochondrial respiration to improve antitumour immunity. The glycolysis pathway in the cytoplasm and the tricarboxylic acid (TCA) cycle in the mitochondria of immune cells provide several therapeutic intervention points. Inhibiting hexokinase 1 (HK1) in the glycolysis pathway promotes T cell memory in vitro. Lactate has harmful effects such as impairing nuclear factor of activated cells (NFAT) and cytokine secretion, and inhibition of lactate dehydrogenase A (LDHA) can reduce lactate production. Lactate secretion can also be blocked by targeting its transporters monocarboxylate transporter 1 (MCT1) and MCT4. Inside mitochondria, enzymes in the acetyl-CoA and TCA cycle can be blocked therapeutically. The TCA cycle intermediate succinate has effects on HIF1α in the nucleus, promoting IL-1β and IL-6 production in macrophages. On the other hand acetyl-CoA enhances histone acetylation to promote T cell memory. Therapeutic interventions are highlighted in red boxes. 2-DG, 2-deoxyglucose; OGDC, 2-oxoglutarate dehydrogenase complex; PCK1, phosphoenolpyruvate carboxykinase 1; MPC1, mitochondrial pyruvate carrier 1; PC, pyruvate carboxylase; PDH, pyruvate dehydrogenase; PHGDH, 3-phosphoglycerate dehydrogenase; GLUT1, glucose transporter 1.

that AZD3965 suppresses T cell proliferation in vitro[159] and MCT1 is required for differentiation of murine memory T cells[166] challenge the premise that MCT1 inhibitors improve cancer immunosurveillance. Nonetheless, synergistic effects of the MCT1 inhibitor AR-C155858 and CAR-T cells have been reported in immunodeficient mice bearing human B cell lymphomas[167]. In these mice, MCT1 inhibition blocks lactate secretion from B cell lymphoma cells (which express only MCT1) but spares CAR-T cells (which express both MCT1 and MCT4)[167]. Of note, many tumour cells express MCT4, which would confer resistance to MCT1 inhibitors[168]. Surprisingly, the anti-inflammatory drug diclofenac inhibits both MCT1 and MCT4 and synergizes with ICB in syngeneic mouse models[169]. Importantly, diclofenac has a minimal impact on T cell activation and proliferation. These results suggest that both single MCT1 inhibition and dual MCT1–MCT4 inhibition can impact tumour cells while preserving some T cell functions.

Lactate has been historically described as an immunosuppressive waste product mainly produced by tumour cells; however, there is growing evidence that it is an energy source for T cells. As lactate is used as a fuel by T cells, excessive levels of NADH — produced by LDHA when it converts lactate into pyruvate — cause reductive stress and inhibit the activity of 3-phosphoglycerate dehydrogenase (PHGDH), which is important for serine production[170]. Interestingly, serine relieved

some of the anti-proliferative effects of lactate on T cells, providing an exciting intervention strategy. Lactate also improves the stem cell properties of $CD8^+$ T cells by regulating epigenetic enzymes[171] and fuels T cell metabolism and differentiation[159]. Lactate also induces a pro-inflammatory phenotype in $CD4^+$ T cells through metabolic rewiring in chronic inflammation[172]. In turn, chronic inflammation impacts tumour control through prostaglandins targeted with non-steroidal anti-inflammatory drugs (NSAIDs)[172] (Box 2). Accordingly, inhibition of mitochondrial pyruvate carrier (MPC) in vivo decreases lactate oxidation and impairs T cell functionality, implying that lactate metabolism supports $CD8^+$ T cell antitumour function[173]. Interestingly, MPC inhibition in T cells cultured ex vivo leads to improved memory formation owing to enhanced glutaminolysis and fatty acid oxidation[173]. Given the complex actions of lactate on T cells, we believe that interventions aimed at this pathway should be investigated in cultured T cells as well as in immunocompetent mouse models.

Mitochondria and TCA cycle intermediates

Inhibitors of mitochondrial OXPHOS have been developed as potential anticancer agents (Fig. 3). Mitochondria are essential organelles for T cell activation, being dynamically regulated throughout T cell differentiation and necessary for the maintenance of T cell memory owing to their involvement in fatty acid oxidation[174–176]. The drug metformin, used to treat diabetes, impacts multiple regulators of mitochondrial metabolism and has been intensely studied in combination with various immunotherapeutic modalities (Box 3). Increasing mitochondrial metabolism through overexpression of the transcriptional coactivator PGC1α improves T cell antitumour activity[177]. Therefore, inhibition of mitochondrial functions to target tumour cells inevitably risks compromising T cell activity. An inhibitor of mitochondrial complex I, IACS-010759, showed efficacy in xenograft models of brain tumours and AML[178] and enhanced antitumour immunity in PD1-resistant syngeneic mouse models of NSCLC[179]. However, two phase I trials investigating IACS-010759 in relapsed or refractory AML or advanced solid tumours were terminated because of dose-limiting toxicities and lack of efficacy[180].

The small molecule CPI-613 (devimistat) inhibits two enzymes that supply substrates to the mitochondrial TCA cycle, 2-oxoglutarate dehydrogenase complex (OGDC) and pyruvate dehydrogenase (PDH)[181] (Fig. 3). Intriguingly, inhibition of PDH with CPI-613 reversed the detrimental effects of lactate (PDH overexpression and pyruvate carboxylase downregulation)[182]. In a phase I clinical study, CPI-613 provided potential clinical benefit in advanced haematological malignancies although it had dose-limiting renal toxicities[183]. A phase III trial (NCT03504423) in patients with metastatic pancreatic adenocarcinoma (PDAC) failed to demonstrate efficacy of CPI-613 in combination with chemotherapy (NCT03504423). CPI-613 is being evaluated in other combinations for the treatment of PDAC (NCT05325281), solid tumours (NCT05733000) and T cell non-Hodgkin lymphomas (NCT04217317). Pending the evaluation of the effects of CPI-613 on immune cells, it remains to be seen whether this inhibitor can stimulate cancer immunosurveillance.

Several TCA cycle intermediates can modulate immune functions, as documented for fumarate, which has immunosuppressive and anti-inflammatory properties and is approved in the form of dimethyl fumarate for the treatment of relapsing–remitting multiple sclerosis[184]. Fumarate accumulates in the TME owing to a deficiency of fumarate hydratase and leads to accumulation of succinate. The succination of ZAP70 kinase, which is essential for T cell receptor signalling, reduced T cell activation and impaired immune control of tumours[185]. Loss-of-function mutation of succinate dehydrogenase similarly leads to the accumulation of succinate, which promotes cancer growth through inhibition of HIF1α hydroxylases[186]. Succinate can also lead to IL-1β production by the upregulation of HIF1α in macrophages[187] (Fig. 3). Accumulation of succinate in the TME has been implicated in the recruitment of macrophages into the tumour and their polarization towards an $IL\text{-}6^+$ tumour-promoting phenotype[188]. These findings imply that strategies to deplete TCA cycle intermediates might promote antitumour immunity.

Microbial metabolites and diet

The intestinal microbiota profoundly affects local and systemic inflammation and immune responses, including the immunosurveillance of cancers across the body[189]. Thus, the interplay between the microbiota and ICB responses has spurred significant interest[189]. For example, the taxonomic composition of the gut microbiota before and after immunotherapy correlates with clinical responses and adverse events in patients with melanoma undergoing ICB[190]. Following pioneering descriptions of a protective role for the microbial metabolite desaminotyrosine against lung viral infections, interest has been sparked in using this 'innate immunometabolite' as an anticancer drug[191] (Fig. 4). Supplementation of mice with desaminotyrosine increased numbers of activated T and NK cells in the TME in a type I interferon-dependent fashion[192]. Another innate immunometabolite, the choline metabolite trimethylamine *N*-oxide (TMAO), also induced type I interferon-dependent inflammatory macrophages in the TME, improving ICB in murine

Box 2 | Prostaglandins

Pro-inflammatory prostaglandins and leukotrienes are bioactive lipids (eicosanoids) produced by the enzymes cyclooxygenase (COX) and lipoxygenase (LOX) in tumour and immune cells[264]. Prostaglandin E_2 (PGE_2) promotes tumour proliferation and invasion in an autocrine and paracrine fashion[264]. Non-steroidal anti-inflammatory drugs (NSAIDs, such as aspirin) inhibit COX2 and are associated with reduced cancer risk in colon, breast, prostate and lung[265]. The impaired T cell priming through dendritic cells caused by PGE_2 can be overcome by inhibiting the COX1 or COX2–PGE_2 axis to enhance the response to anti-programmed cell death protein 1 (PD1) and anti-cytotoxic T lymphocyte-associated protein 4 (CTLA4) immunotherapy[266]. We recently showed that PGE_2 inhibits IL-2 signalling in T cells, limiting stem-like $CD8^+$ T cell expansion and differentiation in the tumour microenvironment and subsequent effector cell functionalities[267]. PGE_2 also induces indoleamine 2,3-dioxygenase 1 (IDO1) expression, linking these two immunosuppressive pathways[268]. Retrospective studies that investigated combinations of COX2 inhibitors with immunotherapy yielded contradictory results, highlighting the need for prospective studies in this regard[269,270]. In the context of hereditary colon cancer (Lynch syndrome), prophylactic COX inhibition by long-term administration of aspirin reduced cancer incidence without increasing adverse events, advocating for the use of aspirin in this patient population[271]. Although there is accumulating retrospective evidence across multiple solid tumour entities indicating that aspirin can prevent cancer development, there is a lack of randomized studies to support its use in a therapeutic setting[272].

models[193]. Oral supplementation of choline to mice induced similar effects in a microbiota-dependent manner, and expression of mRNAs encoding enzymes responsible for TMAO production correlated with survival in patients with PDAC[193]. Likewise, many other microbial metabolites have been shown to act on a range of cancer and immune cells. Given that the intestinal microbiota is impacted by diet, studies on various dietary interventions are being initiated and have indicated that nutrition can have an impact on responses to cancer immunotherapy.

Microbial indoles and dietary tryptophan

Host–microbiota interactions can lead to a surge in immunostimulatory metabolites of tryptophan, in particular, indoles. The microbial product indole-3-acetate (3-IA) is particularly abundant in patients with PDAC responding to chemotherapy[194] (Fig. 4). 3-IA is oxidized by neutrophil myeloperoxidase and inhibits ROS-detoxifying glutathione peroxidases in the context of chemotherapy[194]. Intriguingly, in mice, administration of a tryptophan-enriched diet in conjunction with chemotherapy can increase serum levels of 3-IA[194]. Of note, *Lactobacillus reuteri* can translocate via vascular and lymphatic routes from the gut to the TME of melanomas[195]. Live intratumoural *L. reuteri* bacteria catalyse production of indole-3-carboxyaldehyde (I-3-A) and enhance T cell function in an AHR-dependent manner so that responsiveness to PDL1 blockade is amplified. These effects were enhanced by a tryptophan-enriched diet. Moreover, serum levels of I-3-A predict response to immunotherapy in patients with advanced melanoma[195]. Similarly, indole-3-propionate, which results from metabolic cooperation between *Lactobacillus johnsonii* and *Clostridium sporogenes* in the gut, promotes the cytolysis of cancer cells by $CD8^+$ T cells. This metabolite induces chromatin acetylation and expression of the *Tcf7* gene, which promotes differentiation of the progenitor-exhausted $CD8^+$ T cells that are associated with an anti-PD1 therapy response[196]. Indoles can also reduce therapy-associated side effects. Thus, I-3-A and another tryptophan metabolite, kynurenic acid, which is produced by intestinal Lachnospiraceae, confer protection against whole-body irradiation by promoting haematopoiesis and attenuating gastrointestinal damage[197]. Accordingly, a high relative abundance of Lachnospiraceae and Enterococcaceae was associated with fewer adverse effects[197].

The immunostimulatory effects of microbial AHR agonists — mostly on $CD8^+$ T cells — conflict with the reported immunosuppressive effects of the AHR-activating metabolite kynurenine on T_{reg} cells and MDSCs. Also, knockout or inhibition of AHR in tumour-associated macrophages improved antitumour immunity in murine PDAC models[19]. In such models, a diet high in tryptophan compromised immune control of tumours, because intestinal *Lactobacillus murinus* and *L. reuteri* convert tryptophan into indole-3-lactic acid (3-ILA) and 3-IA, which then activate AHR in tumour-associated macrophages[19] (Fig. 4). This supports the model that AHR agonists exert highly cell- and context-specific effects, and their net effect on cancer immunosurveillance depends on the composition of the tumour[20,21].

Notwithstanding these uncertainties, multiple studies support the crucial role of microbial metabolites on cancer immunosurveillance. Hence, future studies are warranted to investigate the importance of these metabolites in cancer treatments that involve faecal microbial transplantation or supplementation with defined bacteria.

Microbiota and bile acids

Primary bile acids are cholesterol derivatives produced in the liver and released into the intestine, where they are modified by the microbiota

Box 3 | Metformin

Metformin is approved by the FDA for first-line treatment of diabetes mellitus type 2. It is used by several hundred million patients worldwide, improving glycaemic control and reducing mortality with a good safety profile[273]. Adding to its popularity, metformin has been proposed as an anti-ageing drug based on its effects in animal models and retrospective studies in humans[273]. However, its benefits in humans without diabetes are still highly controversial and being studied in prospective clinical trials[273]. The effects of metformin on diabetes were initially attributed to the activation of 5′-AMP-activated protein kinase (AMPK) in the liver[273]. However, AMPK activation is only one of the many described metabolic effects of metformin, which include downregulation of sodium–glucose transporter 1 in the jejunum, inhibition of hexokinase I (HK1), inhibition of NADH-ubiquinone oxidoreductase (mitochondrial respiratory chain 1, complex I) and inhibition of mitochondrial glycerophosphate dehydrogenase[273,274]. Metformin also reshapes the taxonomic composition of the gut microbiota, although with unclear clinical relevance[275]. Interestingly, metformin has anti-inflammatory effects including the reduction of serum TNFα and IL-6 (ref. 273).

Multiple preclinical studies have described antitumour effects for metformin, which depend on immune mechanisms[274,276]. Metformin also destabilizes programmed cell death 1 ligand 1 (PDL1), reduces immunosuppressive macrophage polarization and reduces infiltration of cancers by myeloid-derived suppressor cells[274]. However, most of these effects appear to be mediated through its impact on tumour cells[274]. In patients with oesophageal squamous cell carcinoma, low-dose metformin inhibited STAT3 activation, TNFα, interferon-γ (IFNγ) and IL-10 in peripheral immune cells but increased the number of tumour-infiltrating $CD8^+$ T cells[277]. Several retrospective analyses indicate that patients who received metformin had higher response rates to immune checkpoint blockade (ICB)[276,278]. However, no prospective clinical trial has been conducted to provide evidence for a benefit of metformin in combination with ICB[279]. Metformin without immunotherapy was tested in a randomized double-blinded phase II trial in patients with advanced pancreatic cancer[280], but this trial failed to yield any survival benefit. Similarly, in the phase III MA.32 clinical trial, metformin treatment for 5 years in high-risk patients with metastatic breast cancer failed to extend disease-free survival[281]. Furthermore, the metformin-treated patients had increased grade 3 non-haematological toxic events[281]. The only benefit of metformin was observed in a subgroup of patients with $HER2^+$ breast cancers carrying the C allele of the *rs11212617* genotype[281], replicating an earlier beneficial metformin response affecting this population[282]. These trials indicate that specific patient subpopulations might benefit from metformin in standard-of-care settings. Prospectively, studies of the effects of metformin in combination with cancer immunotherapy are urgently awaited.

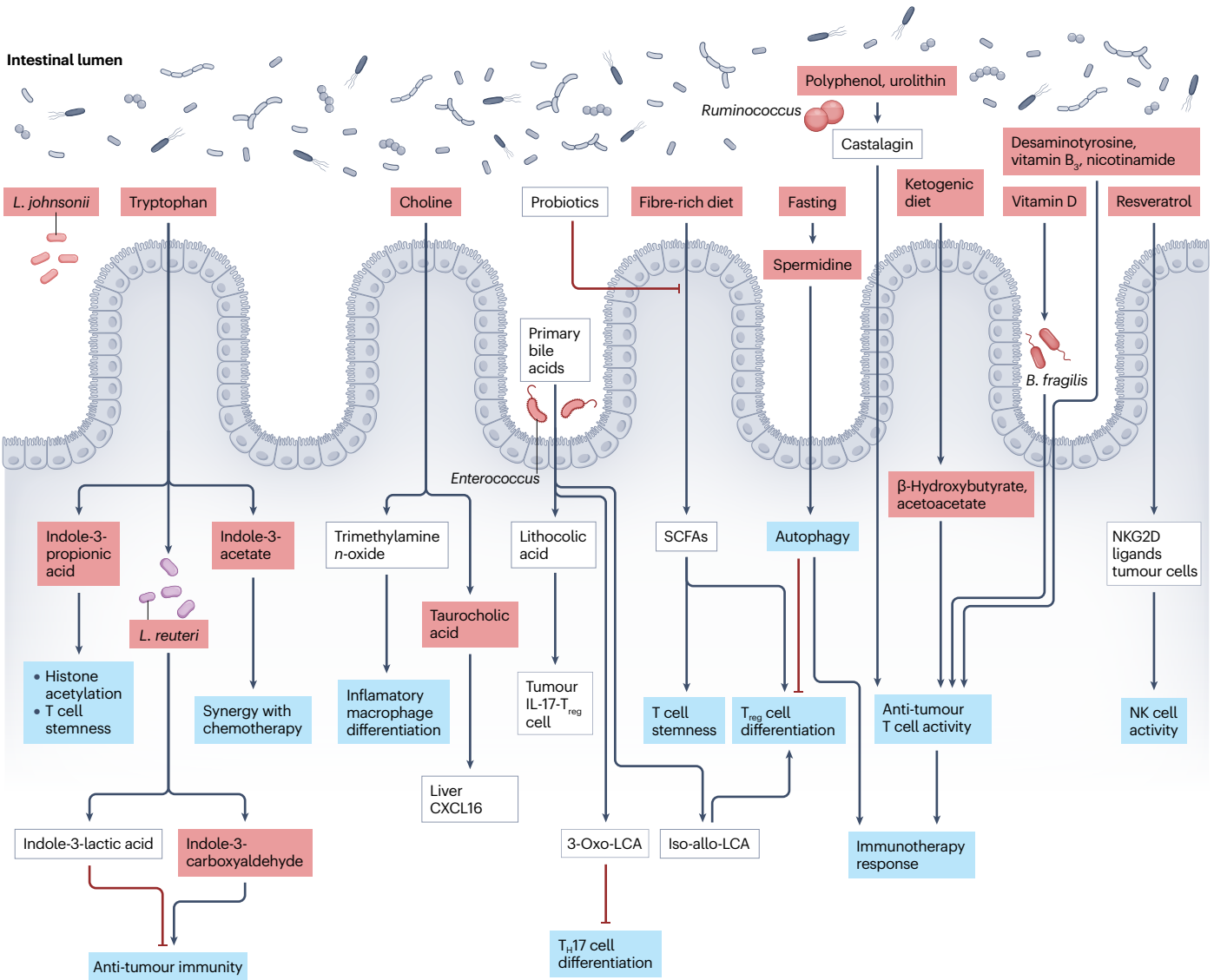

Fig. 4 | Effects of microbiota, nutrition and fasting on the tumour microenvironment. Within the intestinal lumen, the gut microbiota produces various metabolites that are transported to the liver, various lymphoid organs and tumours. Tryptophan can be metabolized by the microbiota into multiple indole derivatives, such as indole-3-propionic acid. Indole derivatives produced by intestinal and intratumoural *Lactobacillus reuteri* bacterial populations can both positively and negatively impact antitumour immunity. Similarly, various primary and secondary bile acids modulate antitumour immunity through effects on T cell differentiation. A fibre-rich diet leads to increased short-chain fatty acid (SCFA) uptake in the intestine and promotes T cell stemness but also regulatory T cell (T_{reg} cell) differentiation. Additionally, spermidine, a compound that is increased during fasting, has potent effects on autophagy and thereby immunotherapy response. Similarly, a ketogenic diet increases β-hydroxybutyrate production, which can promote antitumour immunity via T cell activity. Polyphenols such as urolithin metabolized by *Ruminococcus* species can ameliorate T cell differentiation. Lastly, the polyphenol compound resveratrol can induce ligands for the activating natural killer (NK) receptor NKG2D and thereby induce antitumour activity. Potential therapeutic interventions are highlighted in red boxes. *B. fragilis*, *Bacteroides fragilis*; LCA, lithocholic acid; *L. johnsonii*, *Lactobacillus johnsonii*; PDL1, programmed cell death 1 ligand 1; T_H17 cell, T helper 17.

into secondary bile acids. Bile acids have essential functions in digestion and also signal through receptors such as the farnesoid X receptor (FXR)[198]. Primary bile acids such as taurocholic acid stimulate secretion of the chemokine CXCL16 by liver sinusoidal endothelial cells, and CXCL16 is essential for the recruitment of natural killer T (NKT) cells and antitumour surveillance in the liver[199]. Primary bile acids correlated positively, but secondary bile acids negatively, with the abundance of CXCL16 in liver samples from patients with hepatocellular carcinoma or cholangiocarcinoma[199]. Antibiotic treatment that removed secondary bile acid-producing Gram-positive bacteria from the mouse gut enhanced accumulation of NKT cells and inhibited growth of intrahepatic tumours[199]. The secondary bile acid lithocholic

acid (LCA) and 3-oxo-LCA suppress T helper 17 (T_H17) cell differentiation, and iso-allo-LCA induces T_{reg} cell differentiation through FOXP3 transcriptional regulation[200] (Fig. 4). Intriguingly, antibiotic treatment leads to recolonization of the ileum with bacteria that increase levels of LCA, which downregulates expression of the cell adhesion molecule MADCAM1 (ref. 201). MADCAM1 downregulation drives the migration of certain leukocytes — including IL-17-producing T_{reg} cells — away from the ileum into tumours, an effect that is linked to poor outcome of immunotherapy[201].

In a model of allogeneic bone marrow transplantation, T cell activation depended on the balance between host and microbial bile acids engaging T cell FXR, with ursodeoxycholic acid acting as an anti-inflammatory FXR antagonist. Ablation of FXR expression in T cells blunted graft-versus-host disease (GvHD) in mice[202]. The clinical relevance of these observations is supported by the success of UCDA in reducing GvHD and increasing survival in a clinical trial that prospectively enrolled patients who were receiving allogenic stem cells, mostly owing to malignant disease[203]. These studies collectively highlight the crucial role of bile acids in the microbial regulation of inflammation, which is potentially relevant for colon and liver cancers.

In the large Polyp Prevention Trial, serum bile acids were measured in patients with surgically removed colorectal adenomatous polyps who underwent dietary interventions over the course of 4 years[204]. Baseline bile acid concentrations positively correlated with adenoma recurrence and cancer-associated microbiota features[204]. However, a randomized high-fibre, high-fruit and vegetable, low-fat diet did not alter bile acid levels[204], showing the difficulty of achieving changes in microbial metabolites with dietary interventions. Better strategies are needed to effectively modulate the composition and abundance of secondary bile acids in favour of immunotherapeutic success.

Diet and short-chain fatty acids

Intuitively, the most straightforward and safest way to modulate the intestinal microbiota and its metabolites is through diet. Fasting, dietary interventions and caloric-restriction mimetics are gaining increased attention for their immunomodulatory properties[205,206]. Many short-chain fatty acids (SCFAs), including butyrate, propionate and pentanoate, are mainly produced via fermentation of fibre and starch by the gut microbiota[207]. Commensal bacteria produce these SCFAs and promote T_{reg} cell differentiation in a healthy, non-inflamed colon immune compartment[208–210] (Fig. 4). Systemic levels of SCFAs have been associated with decreased responsiveness to CTLA4 ICB[211], although another study described a positive correlation between faecal SCFAs and PD1 blockade efficacy[212]. Dietary fibre intake also correlated with immunotherapy response in melanoma, a correlation inhibited by the unprescribed use of over-the-counter probiotics[213]; the connection to SCFAs in this study is unclear[213]. In a randomized study in healthy adults, a dietary intervention based on resistant starch, inulin and vinegar increased faecal and serum SCFA levels[214]. The ongoing DIET clinical trial is investigating a high-fibre diet in combination with ICB in melanoma and renal cell cancer (NCT04645680)[215]. It will be important to further dissect the contribution of SCFAs to the effects of high-fibre diets and their relationship to other metabolites[207]. In vitro SCFA supplementation during expansion of CAR-T cells improves their function[216], again highlighting how the ex vivo application of metabolites could be a potential clinical avenue.

SCFAs such as acetate are an alternative carbon source for T cells and tumour cells growing in conditions of low glucose or glycolysis restriction[217,218]. Interestingly, acetate is imported through the same MCT transporters that import lactate[217]. Once inside cells, acetate is converted into acetyl-Co-A by acetyl-CoA synthetase 2 (ACSS2)[217]. Functionally, acetate supplementation promotes histone acetylation and IFNγ expression in T cells in culture[217] (Fig. 3). Also, increased acetate levels in the serum during infections improve the function of memory $CD8^+$ T cells[219]. As a potential therapeutic approach, blockade of ACSS2, which is required for acetate consumption by tumour cells, augments the availability of acetate to T cells and stimulates T cell immunity against breast cancer in animal models[220].

Ketogenic diet

Ketogenic diets contain high fat, moderate protein and low carbohydrates (usually less than 40 g per day). The absence of carbohydrate induces a surge in ketone bodies — in particular 3-hydroxybutyrate (3HB) and acetoacetate — which favours mitochondrial respiration instead of glycolysis for energy metabolism[221]. Ketogenic diets were initially proposed as an intervention to help combat cancer based on direct effects of glucose starvation on cancer cells[222]. However, ketone bodies also act on the immune system. For example, 3HB and acetoacetate increase $CD8^+$ T cell function and improve antitumour immunity[222] (Fig. 4). Similarly, a fasting-mimicking diet was shown to improve responses to ICB, while reducing cardiovascular side effects[223]. Mechanistically, ketogenic diet or supplementation of 3HB in an intermittent schedule was shown to inhibit upregulation of PDL1 on myeloid cells and favour expansion of $CXCR3^+$ T cells associated with antitumour effector functions[224]. Several randomized clinical studies have investigated the impact of a ketogenic diet in patients with breast cancer. A ketogenic diet administered for more than 1 month was well tolerated and achieved elevated serum 3HB concentrations[225] and reductions in body weight and fat mass, whereas muscle mass was preserved[225]. In another study, 12 weeks of ketogenic diet during chemotherapy lowered serum insulin and led to tumour size reduction compared with control, an encouraging finding that needs to be replicated[226]. Decreased TNFα and increased IL-10 in the serum suggested an impact on inflammation[226]. These studies suggest that a ketogenic diet can achieve systemic metabolic changes, thereby enhancing the antitumour effects of chemotherapy. A clinical study investigating the adoption of a ketogenic diet during ICB in patients with metastatic RCC (NCT05119010) was recently terminated owing to recruitment challenges.

Unexpectedly, a recent preclinical study uncovered that a ketogenic diet favoured tumour metastasis via the transcription factor BACH1 in malignant cells[227]. This finding lacks replication and investigation in human studies. Nevertheless, it urges caution with ketogenic diets, especially in non-metastatic disease.

Polyphenols

Pomegranates rich in the polyphenol ellagic acid, a precursor of urolithin A, are often promoted as a 'super-food' by the lay press. Oral supplementation of urolithin A improves anticancer T cell immunity in preclinical models. In vitro, urolithin A facilitates expansion of a stem cell-like CAR-T cell pool by stimulating mitophagy[228]. Furthermore, a urolithin A precursor castalagin, from the camu-camu berry (*Myrciaria dubia*), was shown to improve the outcome of immunotherapy in preclinical models, correlating with the expansion of intestinal *Ruminococcus* species[229] (Fig. 4). A dietary intake of camu-camu powder is being tested in addition to standard-of-care immunotherapy in a phase I trial in patients with advanced NSCLC or melanoma (NCT05303493). In a randomized clinical study with healthy volunteers,

urolithin A supplementation was safe and increased peripheral lymphocytes and NK cells[230]. It also reduced pro-inflammatory cytokines and induced changes in immune phenotypes[230]. Although these effects on immune cells are encouraging, effects on antitumour immunity need to be studied in patients.

Resveratrol is another polyphenol found in various plants, including grapes and berries[231]. Its many reported effects include the induction of stress ligands that stimulate NK cells through the activating receptor NKG2D (also known as KLRK1)[231] (Fig. 4). Moreover, direct immunostimulatory effects of resveratrol on cytokine secretion have been described[231]. Its appropriate dosing is debated, with pharmacologically active concentrations usually far exceeding the doses achievable by red wine consumption for example[232]. A human phase I study established a nonlinear dose–response for resveratrol, indicating that lower doses might have anticancer effects[232]. However, clinical evidence for synergistic effects of resveratrol and immunotherapy is lacking.

Spermidine

Spermidine is a naturally occurring polyamine upregulated by fasting or caloric restriction, and it can induce autophagy and enhance longevity in various animals[233]. Fasting, or administration of the caloric-restriction mimetics spermidine and hydroxycitrate, leads to autophagy-dependent depletion of T_{reg} cells in fibrosarcoma and lung cancer models[234]. Of note, the extension of healthspan and lifespan in model organisms by fasting or caloric restriction depends on the increased spermidine synthesis and the hypusination of eukaryotic initiation factor 5A (eiF5A), which leads to eiF5A-dependent translation of the pro-autophagic transcription factor TFEB and stimulation of autophagic flux[235]. Hypothetically, an age-associated reduction in spermidine levels could explain a corresponding decline in autophagic flux that in turns favours the ageing process by affecting the immune system[233]. Accordingly, spermidine can activate the eiF5A hypusination–autophagy pathway to rejuvenate human B and T lymphocytes from aged human donors in vitro[236,237]. Both fasting and oral spermidine supplementation enhance the efficacy of a combination of chemotherapy that induces immunogenic cell death plus PD1 blockade in syngeneic mouse models[238] (Fig. 4).

Alternative mechanisms to eiF5A hypusination have been suggested to explain the pro-immunosurveillance effects of spermidine supplementation. For example, spermidine inhibits the acetyltransferase EP300 to stimulate autophagy[239], and correspondingly the EP300 inhibitor C646 enhances efficacy of immunogenic chemotherapy[234]. Moreover, spermidine can increase fatty acid oxidation by enhancing the activity of mitochondrial trifunctional protein[240]. The increased fatty acid oxidation favours proliferation, mitochondrial respiration and cytokine production by T cells, and synergizes with PDL1 blockade in aged mice[240]. These findings indicate that spermidine has a multipronged effect on the immune system. Oral supplementation with highly purified spermidine (trihydrochloride spermidine) has been evaluated in healthy volunteers and is well tolerated[241]. However, only spermine — a degradation product of spermidine — was elevated in the plasma of treated individuals[241]. Hence, further studies are required to determine the optimal dosing of spermidine and to test potential immunostimulatory effects in patients.

B and D vitamins

Vitamins derived from diet, supplementation or commensal species in the gut might help to boost antitumour immune responses. This applies to B vitamins, which are produced at least in part by the microbiota. Supplementation with nicotinamide, the amide form of vitamin B_3 and a precursor of NAD^+, prevents ultraviolet light-induced skin cancers in mice and in human transplant recipients[242]. Oral treatment of mice with nicotinamide also retards carcinogenesis of luminal B breast cancers through an increase in immunosurveillance mediated by NK and T cells. Furthermore, vitamin B_3 sensitizes PDAC to gemcitabine-based chemotherapy in a $CD4^+$ T cell-dependent manner[243,244]. Of note, NK cells cultured in vitro with nicotinamide exhibit elevated glucose flux, protection from oxidative stress, enhanced cytotoxic activity and increased cytokine production, thus increasing the clinical efficacy of NK cell transfer into patients with non-Hodgkin lymphoma[245].

Other B vitamins are also endowed with immunomodulatory functions. Vitamin B_5 (pantothenate), a precursor of CoA, reprogrammes T cells towards OXPHOS, differentiates them towards IL-22-producing $CD8^+$ T cells and enhances efficacy of anti-PDL1 antibody therapy in mice[246]. Vitamin B_6 (pyrodoxin) is required for efficient antitumour immune responses[247]. Vitamin B_{12} (cobalamin) produced by the gut microbiota acts as a limiting factor for tissue repair; for example, in experimental colitis it contributes to one-carbon metabolism and the histone methylation required for epigenetic reprogramming[248]. However, high plasma concentrations of vitamin B_{12} are clinically associated with poor outcome of immunotherapy treatments[249]. A systematic review of the impact of B vitamin supplementation on cancer risk found contradictory effects, especially for B_6 and B_9 (ref. 250). Given that B vitamin supplementation is widely used, the unclear effects on cancer risk and as a therapy warrant thorough mechanistic investigations and prospective clinical trials.

Vitamin D exerts regulatory roles through the vitamin D receptor (VDR), which is a transcription factor expressed by intestinal epithelial cells. VDR activation results in taxonomic shifts in the microbiota, with consequences on mucosal immunity, host defence, inflammation and immunity. Mice with a conditional knockout of VDR in intestinal epithelial cells harbour altered microbiota and metabolome (with increased secondary bile acids), as well as exacerbated signalling through the JAK2–STAT3 pathway, culminating in colon carcinogenesis[251]. By contrast, vitamin D exerted immunostimulatory effects by improving the T cell-mediated suppression of transplantable melanomas and synergistic responses to checkpoint blockade in mice[252]. This effect of vitamin D was associated with expansion of *Bacteroides fragilis* in the mouse intestine, and oral gavage of this bacterium was sufficient to confer the melanoma-resistant phenotype[252] (Fig. 4).

Large studies have correlated low 25-hydroxyvitamin D levels and genetic polymorphisms in the vitamin D pathway and biosynthesis genes with cancer mortality[253]. Given its many positive effects, vitamin D supplementation has been studied in multiple large clinical trials. However, in the prospective D-Health clinical trial, no significant benefit of vitamin D supplementation on mortality was found[254]. In a subgroup analysis excluding an early follow-up period, cancer mortality was even increased with vitamin D supplementation. By contrast, in the prospective VITAL clinical trial, a significant reduction of advanced cancers was observed in the vitamin D-treated group, especially in individuals with a body mass index of less than 25 (ref. 255). In a smaller clinical study in patients with advanced cancer receiving ICB, vitamin D supplementation mostly corrected a vitamin deficiency that was found in 94% of patients[256] and the supplemented cohort achieved longer overall survival. In summary, these contradictory studies show that the benefit of vitamin D supplementation in an unscreened general population is uncertain, and prospective randomized trials of vitamin D in cancer immunotherapy warrant further consideration.

Concluding remarks

Tumour cell metabolism offers seemingly unlimited potential for therapeutic interventions, and many potential drugs have been clinically tested. However, historically these agents have been developed with little attention to their immune-related side effects. We argue that this immune-agnostic approach could explain the high failure rate of certain inhibitors in clinical trials, such as those targeting mitochondrial enzymes, glycolysis or lactate secretion. However, several drugs specifically targeting immunosuppressive pathways, such as IDO1 or A_2 inhibitors, have also lacked efficacy. This raises the question of whether better model systems need to be developed instead of the current mouse models typically based on the inoculation of cancer cell lines. That said, the approval of ivosidenib for mIDH1-AML and an impressive phase III study of vorasidenib in mIDH grade 2 glioma exemplify that metabolism inhibitors can be safe and efficacious, even if these examples target mutant enzymes. Many ongoing clinical trials offer promising avenues, including the phase III study investigating the CD73-targeting antibody oleclumab.

The termination of multiple trials investigating the combination of A_2 adenosine receptor inhibitors with checkpoint blockade suggest that ICB might not be the ideal partner for all metabolic interventions. Recent years have revealed several new resistance mechanisms that might enable superior combination strategies, such as glutaminolysis inhibitors with mTOR inhibition or adenosine with IDO1 inhibition. Synthetic metabolic lethality is an exciting new concept in the field of cancer immunotherapy. We anticipate that systematic screening approaches or hypothesis-based investigations based on this concept will lead to the design of new combination treatments.

Dietary and microbiota-centred interventions are gaining ever more attraction, and several ongoing trials could pave the way for more investigations in this realm. Preclinical evidence in favour of the immunostimulatory effects of arginine, castalagin, choline, desaminotyrosine, I-3-A, propionic acid, inosine, spermidine and vitamin D are spurring the design of clinical trials in which such metabolites are orally supplemented. However, clinical evidence for most dietary or supplementation regimens is either controversial or inadequate. Although exciting trials are ongoing, we believe that sophisticated PK/PD studies in this area are mostly elusive. Moreover, the biomarker-based selection of adequate patient populations will be key for the successful completion of trials in which immunotherapies are combined with dietary or supplement-based interventions, as well as with more traditional drug candidates.

Another exciting application of metabolism modulators is for the in vitro expansion of cellular therapy products. Many metabolism-targeted agents can improve CAR-T cell function, stemness and in vivo efficacy, which has been documented for DON, inosine, 2-DG, nicotinamide, MPC inhibitors, urolithin or V-9302. The ex vivo use of these compounds as supplements for cell culture abrogates the risks of inadequate pharmacokinetics or unwarranted toxicities, offering unique therapeutic flexibility. Moreover, if clinically successful, such ex vivo manipulations of immunometabolism should pave the way for future in vivo interventions.

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References

1. Atanasov, A. G. et al. Natural products in drug discovery: advances and opportunities. *Nat. Rev. Drug Discov.* **20**, 200–216 (2021).
2. Stine, Z. E., Schug, Z. T., Salvino, J. M. & Dang, C. V. Targeting cancer metabolism in the era of precision oncology. *Nat. Rev. Drug Discov.* **21**, 141–162 (2021).
3. Zitvogel, L., Apetoh, L., Ghiringhelli, F. & Kroemer, G. Immunological aspects of cancer chemotherapy. *Nat. Rev. Immunol.* **8**, 59–73 (2008).
4. Zhu, J. & Thompson, C. B. Metabolic regulation of cell growth and proliferation. *Nat. Rev. Mol. Cell Biol.* **20**, 436–450 (2019).
5. Elia, I. & Haigis, M. C. Metabolites and the tumour microenvironment: from cellular mechanisms to systemic metabolism. *Nat. Metab.* **3**, 21–32 (2021).
6. Martínez-Reyes, I. & Chandel, N. S. Cancer metabolism: looking forward. *Nat. Rev. Cancer* **21**, 669–680 (2021).
7. Warburg, O. The metabolism of carcinoma cells 1. *J. Cancer Res.* **9**, 148–163 (1925).
8. Leone, R. D. & Powell, J. D. Metabolism of immune cells in cancer. *Nat. Rev. Cancer* **20**, 516–531 (2020).
9. Bantug, G. R., Galluzzi, L., Kroemer, G. & Hess, C. The spectrum of T cell metabolism in health and disease. *Nat. Rev. Immunol.* **18**, 19–34 (2018).
10. Ganjoo, S. et al. The role of tumor metabolism in modulating T-Cell activity and in optimizing immunotherapy. *Front. Immunol.* **14**, 1172931 (2023).
11. Vijayan, D., Young, A., Teng, M. W. L. & Smyth, M. J. Targeting immunosuppressive adenosine in cancer. *Nat. Rev. Cancer* **17**, 709–724 (2017).
12. Xue, C. et al. Tryptophan metabolism in health and disease. *Cell Metab.* **35**, 1304–1326 (2023).
13. Alves Costa Silva, C. et al. Influence of microbiota-associated metabolic reprogramming on clinical outcome in patients with melanoma from the randomized adjuvant dendritic cell-based MIND-DC trial. *Nat. Commun.* **15**, 1633 (2024).
14. Prendergast, G. C., Malachowski, W. P., DuHadaway, J. B. & Muller, A. J. Discovery of IDO1 inhibitors: from bench to bedside. *Cancer Res.* **77**, 6795–6811 (2017).
15. Munn, D. H. et al. Inhibition of T cell proliferation by macrophage tryptophan catabolism. *J. Exp. Med.* **189**, 1363–1372 (1999).
16. Meireson, A., Devos, M. & Brochez, L. IDO expression in cancer: different compartment, different functionality? *Front. Immunol.* **11**, 531491 (2020).
17. Mellor, A. L. & Munn, D. H. Ido expression by dendritic cells: tolerance and tryptophan catabolism. *Nat. Rev. Immunol.* **4**, 762–774 (2004).
18. Wang, S., Wu, J., Shen, H. & Wang, J. The prognostic value of IDO expression in solid tumors: a systematic review and meta-analysis. *BMC Cancer* **20**, 471 (2020).
19. Hezaveh, K. et al. Tryptophan-derived microbial metabolites activate the aryl hydrocarbon receptor in tumor-associated macrophages to suppress anti-tumor immunity. *Immunity* **55**, 324–340.e8 (2022).
20. Campesato, L. F. et al. Blockade of the AHR restricts a Treg-macrophage suppressive axis induced by L-kynurenine. *Nat. Commun.* **11**, 4011 (2020).
21. Mezrich, J. D. et al. An interaction between kynurenine and the aryl hydrocarbon receptor can generate regulatory T cells. *J. Immunol.* **185**, 3190–3198 (2010).
22. Opitz, C. A. et al. An endogenous tumour-promoting ligand of the human aryl hydrocarbon receptor. *Nature* **478**, 197–203 (2011).
23. Schramme, F. et al. Inhibition of tryptophan-dioxygenase activity increases the antitumor efficacy of immune checkpoint inhibitors. *Cancer Immunol. Res.* **8**, 32–45 (2020).
24. Liu, Y. et al. Tumor-repopulating cells induce PD-1 expression in CD8+ T cells by transferring kynurenine and AhR activation. *Cancer Cell* **33**, 480–494.e7 (2018).
25. Liu, Y. et al. IL-2 regulates tumor-reactive $CD8^+$ T cell exhaustion by activating the aryl hydrocarbon receptor. *Nat. Immunol.* **22**, 358–369 (2021).
26. Monjazeb, A. M. et al. Blocking indolamine-2,3-dioxygenase rebound immune suppression boosts antitumor effects of radio-immunotherapy in murine models and spontaneous canine malignancies. *Clin. Cancer Res.* **22**, 4328–4340 (2016).
27. Hou, D. Y. et al. Inhibition of indoleamine 2,3-dioxygenase in dendritic cells by stereoisomers of 1-methyl-tryptophan correlates with antitumor responses. *Cancer Res.* **67**, 792–801 (2007).
28. Muller, A. J., DuHadaway, J. B., Donover, P. S., Sutanto-Ward, E. & Prendergast, G. C. Inhibition of indoleamine 2,3-dioxygenase, an immunoregulatory target of the cancer suppression gene Bin1, potentiates cancer chemotherapy. *Nat. Med.* **11**, 312–319 (2005).
29. Holmgaard, R. B., Zamarin, D., Munn, D. H., Wolchok, J. D. & Allison, J. P. Indoleamine 2,3-dioxygenase is a critical resistance mechanism in antitumor T cell immunotherapy targeting CTLA-4. *J. Exp. Med.* **210**, 1389–1402 (2013).
30. Mitchell, T. C. et al. Epacadostat plus pembrolizumab in patients with advanced solid tumors: phase I results from a multicenter, open-label phase I/II trial (ECHO-202/KEYNOTE-037). *J. Clin. Oncol.* **36**, 3223–3230 (2018).
31. Long, G. V. et al. Epacadostat plus pembrolizumab versus placebo plus pembrolizumab in patients with unresectable or metastatic melanoma (ECHO-301/KEYNOTE-252): a phase 3, randomised, double-blind study. *Lancet Oncol.* **20**, 1083–1097 (2019).
32. Lara, P. N. et al. A randomized, open-label, phase 3 trial of pembrolizumab plus epacadostat versus sunitinib or pazopanib as first-line treatment for metastatic renal cell carcinoma (KEYNOTE-679/ECHO-302). *BMC Cancer* **23**, 1253 (2024).
33. Van den Eynde, B. J., van Baren, N. & Baurain, J.-F. Is there a clinical future for IDO1 inhibitors after the failure of epacadostat in melanoma? *Annu. Rev. Cancer Biol.* **4**, 241–256 (2020).
34. Kelly, C. M. et al. A phase II study of epacadostat and pembrolizumab in patients with advanced sarcoma. *Clin. Cancer Res.* **29**, 2043–2051 (2023).
35. Wang, Z. et al. Sphingomyelin-derived nanovesicles for the delivery of the IDO1 inhibitor epacadostat enhance metastatic and post-surgical melanoma immunotherapy. *Nat. Commun.* **14**, 7235 (2023).
36. Odunsi, K. et al. Metabolic adaptation of ovarian tumors in patients treated with an IDO1 inhibitor constrains antitumor immune responses. *Sci. Transl. Med.* **14**, 8402 (2022).
37. Bartok, O. et al. Anti-tumour immunity induces aberrant peptide presentation in melanoma. *Nature* **590**, 332–337 (2021).

38. Saha, S. et al. Serine depletion promotes antitumor immunity by activating mitochondrial DNA-mediated cGAS-STING signaling. *Cancer Res.* **84**, 2645–2659 (2024).
39. Sharma, M. D. et al. Inhibition of the BTK-IDO-mTOR axis promotes differentiation of monocyte-lineage dendritic cells and enhances anti-tumor T cell immunity. *Immunity* **54**, 2354–2371.e8 (2021).
40. Pilotte, L. et al. Reversal of tumoral immune resistance by inhibition of tryptophan 2,3-dioxygenase. *Proc. Natl Acad. Sci. USA* **109**, 2497–2502 (2012).
41. Wu, C. et al. Dual inhibition of IDO1/TDO2 enhances anti-tumor immunity in platinum-resistant non-small cell lung cancer. *Cancer Metab.* **11**, 7 (2023).
42. Sadik, A. et al. IL4I1 is a metabolic immune checkpoint that activates the AHR and promotes tumor progression. *Cell* **182**, 1252–1270.e34 (2020).
43. Bekkat, F. et al. Upregulation of IL4-induced gene 1 enzyme by B2 cells during melanoma progression impairs their antitumor properties. *Eur. J. Immunol.* **54**, e2350615 (2024).
44. Hirose, S. et al. Interleukin-4 induced 1-mediated resistance to an immune checkpoint inhibitor through suppression of CD8+ T cell infiltration in melanoma. *Cancer Sci.* **115**, 791–803 (2024).
45. Zeitler, L. et al. Anti-ferroptotic mechanism of il4i1-mediated amino acid metabolism. *eLife* **10**, e64806 (2021).
46. Metz, R. et al. IDO inhibits a tryptophan sufficiency signal that stimulates mTOR: a novel IDO effector pathway targeted by D-1-methyl-tryptophan. *Oncoimmunology* **1**, 1460–1468 (2012).
47. Fox, E. et al. Indoximod: an immunometabolic adjuvant that empowers T cell activity in cancer. *Front. Oncol.* **8**, 370 (2018).
48. Triplett, T. A. et al. Reversal of indoleamine 2,3-dioxygenase–mediated cancer immune suppression by systemic kynurenine depletion with a therapeutic enzyme. *Nat. Biotechnol.* **36**, 758–764 (2018).
49. Altman, B. J., Stine, Z. E. & Dang, C. V. From Krebs to clinic: glutamine metabolism to cancer therapy. *Nat. Rev. Cancer* **16**, 619–634 (2016).
50. Bott, A. J. et al. Oncogenic myc induces expression of glutamine synthetase through promoter demethylation. *Cell Metab.* **22**, 1068–1077 (2015).
51. Eagle, H., Oyama, V. I., Levy, M., Horton, C. L. & Fleischman, R. The growth response of mammalian cells in tissue culture to L-glutamine and L-glutamic acid. *J. Biol. Chem.* **218**, 607–616 (1956).
52. Welbourne, T. C. Ammonia production and glutamine incorporation into glutathione in the functioning rat kidney. *Can. J. Biochem.* **57**, 233–237 (1979).
53. Liu, P. S. et al. A-ketoglutarate orchestrates macrophage activation through metabolic and epigenetic reprogramming. *Nat. Immunol.* **18**, 985–994 (2017).
54. Liu, N. et al. Supplementation with α-ketoglutarate improved the efficacy of anti-PD1 melanoma treatment through epigenetic modulation of PD-L1. *Cell Death Dis.* **14**, 170 (2023).
55. Klysz, D. et al. Glutamine-dependent α-ketoglutarate production regulates the balance between T helper 1 cell and regulatory T cell generation. *Sci. Signal.* **8**, ra97 (2015).
56. Matias, M. I. et al. Regulatory T cell differentiation is controlled by αKG-induced alterations in mitochondrial metabolism and lipid homeostasis. *Cell Rep.* **37**, 109911 (2021).
57. Jin, J., Byun, J. K., Choi, Y. K. & Park, K. G. Targeting glutamine metabolism as a therapeutic strategy for cancer. *Exp. Mol. Med.* **55**, 706–715 (2023).
58. Emberley, E. et al. The glutaminase inhibitor telaglenastat enhances the antitumor activity of signal transduction inhibitors everolimus and cabozantinib in models of renal cell carcinoma. *PLoS ONE* **16**, e0259241 (2021).
59. Leone, R. D. et al. Glutamine blockade induces divergent metabolic programs to overcome tumor immune evasion. *Science* **366**, 1013–1021 (2019).
60. Oh, M. H. et al. Targeting glutamine metabolism enhances tumor-specific immunity by modulating suppressive myeloid cells. *J. Clin. Invest.* **130**, 3865–3884 (2020).
61. Shen, L. et al. Metabolic reprogramming by ex vivo glutamine inhibition endows CAR-T cells with less-differentiated phenotype and persistent antitumor activity. *Cancer Lett.* **538**, 215710 (2022).
62. Byun, J. K. et al. Inhibition of glutamine utilization synergizes with immune checkpoint inhibitor to promote antitumor immunity. *Mol. Cell* **80**, 592–606.e8 (2020).
63. Nakazawa, M. et al. Glutamine antagonist DRP-104 in combination with durvalumab in patients with advanced fibrolamellar carcinoma (FLC) following progression on prior anti-PD(L)1 therapy. *J. Clin. Oncol.* **42**, TPS573 (2024).
64. Yap, T. A. et al. First-in-human biomarker-driven phase I trial of the potent and selective glutaminase-1 (GLS1) inhibitor IACS-6274 (IPN60090) in patients (pts) with molecularly selected advanced solid tumors. *J. Clin. Oncol.* **39**, 3001 (2021).
65. Varghese, S. et al. The glutaminase inhibitor CB-839 (Telaglenastat) enhances the antimelanoma activity of T-cell-mediated immunotherapies. *Mol. Cancer Ther.* **20**, 500–511 (2021).
66. Best, S. A. et al. Glutaminase inhibition impairs CD8 T cell activation in STK11-/Lkb1-deficient lung cancer. *Cell Metab.* **34**, 874–887.e6 (2022).
67. Davidson, S. M. et al. Environment impacts the metabolic dependencies of Ras-driven non-small cell lung cancer. *Cell Metab.* **23**, 517–528 (2016).
68. Tannir, N. M. et al. Efficacy and safety of telaglenastat plus cabozantinib vs placebo plus cabozantinib in patients with advanced renal cell carcinoma: the CANTATA randomized clinical trial. *JAMA Oncol.* **8**, 1411–1418 (2022).
69. Romero, R. et al. Keap1 loss promotes Kras-driven lung cancer and results in dependence on glutaminolysis. *Nat. Med.* **23**, 1362–1368 (2017).
70. Durán, R. V. & Hall, M. N. Glutaminolysis feeds mTORC1. *Cell Cycle* **11**, 4107–4108 (2012).
71. Lee, C. H. et al. Telaglenastat plus everolimus in advanced renal cell carcinoma: a randomized, double-blinded, placebo-controlled, phase II ENTRATA trial. *Clin. Cancer Res.* **28**, 3248–3255 (2022).
72. Levi, J. & Song, H. The other immuno-PET: metabolic tracers in evaluation of immune responses to immune checkpoint inhibitor therapy for solid tumors. *Front. Immunol.* **13**, 1113924 (2023).
73. Dixon, S. J. & Olzmann, J. A. The cell biology of ferroptosis. *Nat. Rev. Mol. Cell Biol.* **25**, 424–442 (2024).
74. Sinclair, L. V. et al. Control of amino-acid transport by antigen receptors coordinates the metabolic reprogramming essential for T cell differentiation. *Nat. Immunol.* **14**, 500–508 (2013).
75. Guo, C. et al. SLC38A2 and glutamine signalling in cDC1s dictate anti-tumour immunity. *Nature* **620**, 200–208 (2023).
76. Reinfeld, B. I. et al. Cell-programmed nutrient partitioning in the tumour microenvironment. *Nature* **593**, 282–288 (2021).
77. Edwards, D. N. et al. Selective glutamine metabolism inhibition in tumor cells improves antitumor T lymphocyte activity in triple-negative breast cancer. *J. Clin. Invest.* **131**, e140100 (2021).
78. Bröer, A., Fairweather, S. & Bröer, S. Disruption of amino acid homeostasis by novel ASCT2 inhibitors involves multiple targets. *Front. Pharmacol.* **9**, 388915 (2018).
79. Han, S. et al. IDH mutation in glioma: molecular mechanisms and potential therapeutic targets. *Br. J. Cancer* **122**, 1580–1589 (2020).
80. Pirozzi, C. J. & Yan, H. The implications of IDH mutations for cancer development and therapy. *Nat. Rev. Clin. Oncol.* **18**, 645–661 (2021).
81. Dang, L. et al. Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. *Nature* **462**, 739–744 (2009).
82. Notarangelo, G. et al. Oncometabolite D-2HG alters T cell metabolism to impair CD8+ T cell function. *Science* **377**, 1519–1529 (2022).
83. Bunse, L. et al. Suppression of antitumor T cell immunity by the oncometabolite (*R*)-2-hydroxyglutarate. *Nat. Med.* **24**, 1192–1203 (2018).
84. Hammon, K. et al. D-2-hydroxyglutarate supports a tolerogenic phenotype with lowered major histocompatibility class II expression in non-malignant dendritic cells and acute myeloid leukemia cells. *Haematologica* **109**, 2500–2514 (2024).
85. Wu, M. J. et al. Mutant IDH inhibits IFNγ–TET2 signaling to promote immunoevasion and tumor maintenance in cholangiocarcinoma. *Cancer Discov.* **12**, 812–835 (2022).
86. Tian, W. et al. Recent advances of IDH1 mutant inhibitor in cancer therapy. *Front. Pharmacol.* **13**, 982424 (2022).
87. Montesinos, P. et al. Ivosidenib and azacitidine in IDH1-mutated acute myeloid leukemia. *N. Engl. J. Med.* **386**, 1519–1531 (2022).
88. Mellinghoff, I. K. et al. Vorasidenib in IDH1- or IDH2-mutant low-grade glioma. *N. Engl. J. Med.* **389**, 589–601 (2023).
89. Kadiyala, P. et al. Inhibition of 2-hydroxyglutarate elicits metabolic reprogramming and mutant IDH1 glioma immunity in mice. *J. Clin. Invest.* **131**, e139542 (2021).
90. Friedrich, M. et al. Tryptophan metabolism drives dynamic immunosuppressive myeloid states in IDH-mutant gliomas. *Nat. Cancer* **2**, 723–740 (2021).
91. Tyrakis, P. A. et al. S-2-hydroxyglutarate regulates $CD8^+$ T-lymphocyte fate. *Nature* **540**, 236–241 (2016).
92. Minogue, E. et al. Glutarate regulates T cell metabolism and anti-tumour immunity. *Nat. Metab.* **5**, 1747–1764 (2023).
93. Morris, S. M. Arginine metabolism revisited. *J. Nutr.* **146**, 2579S–2586S (2016).
94. Grzywa, T. M. et al. Myeloid cell-derived arginase in cancer immune response. *Front. Immunol.* **11**, 938 (2020).
95. Geiger, R. et al. L-arginine modulates T cell metabolism and enhances survival and anti-tumor activity. *Cell* **167**, 829–842.e13 (2016).
96. Mazzoni, A. et al. Myeloid suppressor lines inhibit T cell responses by an NO-dependent mechanism. *J. Immunol.* **168**, 689–695 (2002).
97. Cao, Y., Feng, Y., Zhang, Y., Zhu, X. & Jin, F. L-Arginine supplementation inhibits the growth of breast cancer by enhancing innate and adaptive immune responses mediated by suppression of MDSCs in vivo. *BMC Cancer* **16**, 343 (2016).
98. Naing, A. et al. First-in-human phase 1 study of the arginase inhibitor INCB001158 alone or combined with pembrolizumab in patients with advanced or metastatic solid tumours. *BMJ Oncol.* **3**, e000249 (2024).
99. Kuboki, Y. et al. PD-1 inhibition with retifanlimab and/or arginase inhibition with INCB001158 in Japanese patients with solid tumors: a phase I study. *Cancer Med.* **13**, e6980 (2024).
100. Borek, B. et al. Arginase 1/2 inhibitor OATD-02: from discovery to first-in-man setup in cancer immunotherapy. *Mol. Cancer Ther.* **22**, 807–817 (2023).
101. Nishio, S. I. et al. The effect of taurine on age-related immune decline in mice: the effect of taurine on T cell and B cell proliferative response under costimulation with ionomycin and phorbol myristate acetate. *Mech. Ageing Dev.* **52**, 125–139 (1990).
102. Maher, S. G., Condron, C. E. M., Bouchier-Hayes, D. J. & Toomey, D. M. Taurine attenuates CD3/interleukin-2-induced T cell apoptosis in an in vitro model of activation-induced cell death (AICD). *Clin. Exp. Immunol.* **139**, 279–286 (2004).
103. Kaesler, S. et al. Effective T-cell recall responses require the taurine transporter Taut. *Eur. J. Immunol.* **42**, 831–841 (2012).
104. Ping, Y. et al. Taurine enhances the antitumor efficacy of PD-1 antibody by boosting CD8+ T cell function. *Cancer Immunol., Immunother.* **72**, 1015–1027 (2023).
105. Cao, T. et al. Cancer SLC6A6-mediated taurine uptake transactivates immune checkpoint genes and induces exhaustion in CD8+ T cells. *Cell* **187**, 2288–2304.e27 (2024).

106. Huang, D. et al. Cancer-cell-derived GABA promotes β-catenin-mediated tumour growth and immunosuppression. *Nat. Cell Biol.* **24**, 230–241 (2022).
107. Zhang, B. et al. B cell-derived GABA elicits IL-10+ macrophages to limit anti-tumour immunity. *Nature* **599**, 471–476 (2021).
108. Montégut, L. et al. Acyl-coenzyme a binding protein (ACBP) - a risk factor for cancer diagnosis and an inhibitor of immunosurveillance. *Mol. Cancer* **23**, 187 (2024).
109. Herr, N., Bode, C. & Duerschmied, D. The effects of serotonin in immune cells. *Front. Cardiovasc. Med.* **4**, 48 (2017).
110. Lesurtel, M., Soll, C., Graf, R. & Clavien, P. A. Role of serotonin in the hepato-gastroIntestinal tract: an old molecule for new perspectives. *Cell. Mol. Life Sci.* **65**, 940–952 (2008).
111. Schneider, M. A. et al. Attenuation of peripheral serotonin inhibits tumor growth and enhances immune checkpoint blockade therapy in murine tumor models. *Sci. Transl. Med.* **13**, 8188 (2021).
112. Bi, J. et al. Targeting glioblastoma signaling and metabolism with a re-purposed brain-penetrant drug. *Cell Rep.* **37**, 109957 (2021).
113. Di Virgilio, F., Sarti, A. C., Falzoni, S., De Marchi, E. & Adinolfi, E. Extracellular ATP and P2 purinergic signalling in the tumour microenvironment. *Nat. Rev. Cancer* **18**, 601–618 (2018).
114. Allard, B., Allard, D., Buisseret, L. & Stagg, J. The adenosine pathway in immuno-oncology. *Nat. Rev. Clin. Oncol.* **17**, 611–629 (2020).
115. Horenstein, A. L. et al. Adenosine generated in the bone marrow niche through a CD38-mediated pathway correlates with progression of human myeloma. *Mol. Med.* **22**, 694–704 (2016).
116. Ohta, A. et al. A2A adenosine receptor protects tumors from antitumor T cells. *Proc. Natl Acad. Sci. USA* **103**, 13132 (2006).
117. Stagg, J. et al. CD73-deficient mice have increased antitumor immunity and are resistant to experimental metastasis. *Cancer Res.* **71**, 2892–2900 (2011).
118. Hay, C. M. et al. Targeting CD73 in the tumor microenvironment with MEDI9447. *Oncoimmunology* **5**, e1208875 (2016).
119. Herbst, R. S. et al. COAST: an open-label, phase II, multidrug platform study of durvalumab alone or in combination with oleclumab or monalizumab in patients with unresectable, stage III non-small-cell lung cancer. *J. Clin. Oncol.* **3**, 3383–3393 (2022).
120. Bendell, J. et al. First-in-human study of oleclumab, a potent, selective anti-CD73 monoclonal antibody, alone or in combination with durvalumab in patients with advanced solid tumors. *Cancer Immunol., Immunother.* **72**, 2443–2458 (2023).
121. Piovesan, D. et al. Targeting CD73 with AB680 (Quemliclustat), a novel and potent small-molecule CD73 inhibitor, restores immune functionality and facilitates antitumor immunity. *Mol. Cancer Ther.* **21**, 948–959 (2022).
122. Wainberg, Z. A. et al. ARC-8: phase 1/1b randomized study of quemliclustat + gemcitabine/nab-paclitaxel ± zimberelimab in patients with treatment-naive metastatic pancreatic adenocarcinoma. *J. Clin. Oncol.* **42** (suppl. 3), Abstr. 665 (2024).
123. Siu, L. L. et al. Preliminary phase 1 profile of BMS-986179, an anti-CD73 antibody, in combination with nivolumab in patients with advanced solid tumors. *Cancer Res.* **78**, Abstr. CT180 (2018).
124. Luke, J. J. et al. Immunobiology, preliminary safety, and efficacy of CPI-006, an anti-CD73 antibody with immune modulating activity, in a phase 1 trial in advanced cancers. *J. Clin. Oncol.* **37** (suppl. 15), Abstr. 2505 (2019).
125. Li, X. Y. et al. Targeting CD39 in cancer reveals an extracellular ATP-and inflammasome-driven tumor immunity. *Cancer Discov.* **9**, 1754–1773 (2019).
126. Perrot, I. et al. Blocking antibodies targeting the CD39/CD73 immunosuppressive pathway unleash immune responses in combination cancer therapies. *Cell Rep.* **27**, 2411–2425.e9 (2019).
127. Imbimbo, M. et al. 188P. IPH5201 as monotherapy or in combination with durvalumab (D) in advanced solid tumours. *Immuno-Oncol. Technol.* **16**, 100300 (2022).
128. Patnaik, A. et al. 135P. First-in-human phase I trial of SRF617, a potent inhibitor of CD39 activity, as monotherapy or in combination, in patients (pts) with advanced solid tumors. *Ann. Oncol.* **32**, S1435–S1436 (2021).
129. Wainberg, Z. et al. Safety and efficacy of TTX-030, an anti-CD39 antibody, in combination with chemoimmunotherapy for the first line treatment of locally advanced or metastatic gastric/GEJ cancer. *Cancer Res.* **82**, Abstr. CT015 (2022).
130. Wainberg, Z. A. et al. ARC-9: a randomized study to evaluate etrumadenant based treatment combinations in previously treated metastatic colorectal cancer (mCRC). *J. Clin. Oncol.* **42** (suppl. 16), Abstr. 3508 (2024).
131. Fong, L. et al. Adenosine 2A receptor blockade as an immunotherapy for treatment-refractory renal cell cancer. *Cancer Discov.* **10**, 40–53 (2020).
132. Beckermann, D. K., Rini, B., Haas, D. N., George, D. D. & Jonasch, D. E. Phase 1b/2 trial of ipilimumab, nivolumab, and ciforadenant (INC) (adenosine A2a receptor antagonist) in first-line advanced renal cell carcinoma. *Oncologist* **28**, S13 (2023).
133. Augustin, R. C. et al. Next steps for clinical translation of adenosine pathway inhibition in cancer immunotherapy. *J. Immunother. Cancer* **10**, e004089 (2022).
134. Gordoa, T. A. et al. Phase 2 study (AARDVARC) of AZD4635 in combination with durvalumab and cabazitaxel in patients (pts) with progressive metastatic castrate-resistant prostate cancer (mCRPC). *J. Clin. Oncol.* **41** (suppl. 6), Abstr. 173 (2023).
135. Chiappori, A. A. et al. Phase I study of taminadenant (PBF509/NIR178), an adenosine 2A receptor antagonist, with or without spartalizumab (PDR001), in patients with advanced non-small cell lung cancer. *Clin. Cancer Res.* **28**, 2313–2320 (2022).
136. Seifert, M. et al. Impact of the selective A2AR and A2BR dual antagonist AB928/etrumadenant on CAR T cell function. *Br. J. Cancer* **127**, 127 (2022).
137. Klysz, D. D. et al. Inosine induces stemness features in CAR-T cells and enhances potency. *Cancer Cell* **42**, 266–282.e8 (2024).
138. Mager, L. F. et al. Microbiome-derived inosine modulates response to checkpoint inhibitor immunotherapy. *Science* **369**, 1481–1489 (2020).
139. Wang, L. et al. Targeting adenosine with adenosine deaminase 2 to inhibit growth of solid tumors. *Cancer Res.* **81**, 3319–3332 (2021).
140. Lunt, S. Y. & Vander Heiden, M. G. Aerobic glycolysis: meeting the metabolic requirements of cell proliferation. *Annu. Rev. Cell Dev. Biol.* **27**, 441–464 (2011).
141. Pavlova, N. N. & Thompson, C. B. The emerging hallmarks of cancer metabolism. *Cell Metab.* **23**, 27–47 (2016).
142. Ho, P. C. et al. Phosphoenolpyruvate is a metabolic checkpoint of anti-tumor T cell responses. *Cell* **162**, 1217–1228 (2015).
143. Macintyre, A. N. et al. The glucose transporter Glut1 is selectively essential for CD4 T cell activation and effector function. *Cell Metab.* **20**, 61–72 (2014).
144. Chang, C. H. et al. Metabolic competition in the tumor microenvironment is a driver of cancer progression. *Cell* **162**, 1229–1241 (2015).
145. Pajak, B. et al. 2-Deoxy-D-glucose and its analogs: from diagnostic to therapeutic agents. *Int. J. Mol. Sci.* **21**, 234 (2019).
146. Temre, M. K., Kumar, A. & Singh, S. M. An appraisal of the current status of inhibition of glucose transporters as an emerging antineoplastic approach: promising potential of new pan-GLUT inhibitors. *Front. Pharmacol.* **13**, 1035510 (2022).
147. Di Dedda, C., Vignali, D., Piemonti, L. & Monti, P. Pharmacological targeting of GLUT1 to control autoreactive T cell responses. *Int. J. Mol. Sci.* **20**, 4962 (2019).
148. Fu, H. et al. The glucose transporter 2 regulates CD8+ T cell function via environment sensing. *Nat. Metab.* **5**, 1969–1985 (2023).
149. Sukumar, M. et al. Inhibiting glycolytic metabolism enhances CD8+ T cell memory and antitumor function. *J. Clin. Investig.* **123**, 4479–4488 (2013).
150. Cappabianca, D. et al. Metabolic priming of GD2 TRAC-CAR T cells during manufacturing promotes memory phenotypes while enhancing persistence. *Mol. Ther. Methods Clin. Dev.* **32**, 101249 (2024).
151. Araki, K. et al. mTOR regulates memory CD8 T-cell differentiation. *Nature* **460**, 108–112 (2009).
152. Funk, C. R. et al. PI3Kδ/γ inhibition promotes human CART cell epigenetic and metabolic reprogramming to enhance antitumor cytotoxicity. *Blood* **139**, 523–537 (2022).
153. Chan, J. D. et al. FOXO1 enhances CAR T cell stemness, metabolic fitness and efficacy. *Nature* **629**, 201–210 (2024).
154. Alizadeh, D. et al. IL15 enhances CAR-T cell antitumor activity by reducing mTORC1 activity and preserving their stem cell memory phenotype. *Cancer Immunol. Res.* **7**, 759–772 (2019).
155. Watson, M. J. & Delgoffe, G. M. Fighting in a wasteland: deleterious metabolites and antitumor immunity. *J. Clin. Invest.* **132**, e148549 (2022).
156. Certo, M., Tsai, C. H., Pucino, V., Ho, P. C. & Mauro, C. Lactate modulation of immune responses in inflammatory versus tumour microenvironments. *Nat. Rev. Immunol.* **21**, 151–161 (2020).
157. Chang, C. H. et al. Posttranscriptional control of T cell effector function by aerobic glycolysis. *Cell* **153**, 1239 (2013).
158. Brand, A. et al. LDHA-associated lactic acid production blunts tumor immunosurveillance by T and NK cells. *Cell Metab.* **24**, 657–671 (2016).
159. Barbieri, L. et al. Lactate exposure shapes the metabolic and transcriptomic profile of CD8+ T cells. *Front. Immunol.* **14**, 1101433 (2023).
160. Watson, M. L. J. et al. Metabolic support of tumour-infiltrating regulatory T cells by lactic acid. *Nature* **591**, 645–651 (2021).
161. Angelin, A. et al. Foxp3 reprograms T cell metabolism to function in low-glucose, high-lactate environments. *Cell Metab.* **25**, 1282–1293.e7 (2017).
162. Gu, J. et al. Tumor metabolite lactate promotes tumorigenesis by modulating MOESIN lactylation and enhancing TGF-β signaling in regulatory T cells. *Cell Rep.* **39**, 110986 (2022).
163. Cascone, T. et al. Increased tumor glycolysis characterizes immune resistance to adoptive T cell therapy. *Cell Metab.* **27**, 977–987.e4 (2018).
164. Silva, A. et al. In vivo anticancer activity of AZD3965: a systematic review. *Molecules* **27**, 181 (2022).
165. Halford, S. et al. A phase I dose-escalation study of AZD3965, an oral monocarboxylate transporter 1 inhibitor, in patients with advanced cancer. *Clin. Cancer Res.* **29**, 1429–1439 (2023).
166. D'Aria, S. et al. Expression of the monocarboxylate transporter MCT1 is required for virus-specific mouse CD8+ T cell memory development. *Proc. Natl Acad. Sci. USA* **121**, e2306763121 (2024).
167. Lopez, E. et al. Inhibition of lactate transport by MCT-1 blockade improves chimeric antigen receptor T-cell therapy against B-cell malignancies. *J. Immunother. Cancer* **11**, e006287 (2023).
168. Polanski, R. et al. Activity of the monocarboxylate transporter 1 inhibitor azd3965 in small cell lung cancer. *Clin. Cancer Res.* **20**, 926–937 (2014).
169. Renner, K. et al. Restricting glycolysis preserves T cell effector functions and augments checkpoint therapy. *Cell Rep.* **29**, 135–150.e9 (2019).
170. Quinn, W. J. et al. Lactate limits T cell proliferation via the NAD(H) redox state. *Cell Rep.* **33**, 108500 (2020).
171. Feng, Q. et al. Lactate increases stemness of CD8+ T cells to augment anti-tumor immunity. *Nat. Commun.* **13**, 4981 (2022).
172. Pucino, V. et al. Lactate buildup at the site of chronic inflammation promotes disease by inducing CD4+ T cell metabolic rewiring. *Cell Metab.* **30**, 1055 (2019).

173. Wenes, M. et al. The mitochondrial pyruvate carrier regulates memory T cell differentiation and antitumor function. *Cell Metab.* **34**, 731–746.e9 (2022).
174. Buck, M. D. D. et al. Mitochondrial dynamics controls T cell fate through metabolic programming. *Cell* **166**, 63–76 (2016).
175. Lisci, M. et al. Mitochondrial translation is required for sustained killing by cytotoxic T cells. *Science* **374**, eabe9977 (2021).
176. Lisci, M. & Griffiths, G. M. Arming a killer: mitochondrial regulation of CD8+ T cell cytotoxicity. *Trends Cell Biol.* **33**, 138–147 (2023).
177. Scharping, N. E. et al. The tumor microenvironment represses T cell mitochondrial biogenesis to drive intratumoral T cell metabolic insufficiency and dysfunction. *Immunity* **45**, 374–388 (2016).
178. Molina, J. R. et al. An inhibitor of oxidative phosphorylation exploits cancer vulnerability. *Nat. Med.* **24**, 1036–1046 (2018).
179. Chen, D. et al. Combination treatment with radiotherapy and a novel oxidative phosphorylation inhibitor overcomes PD-1 resistance and enhances antitumor immunity. *J. Immunother. Cancer* **8**, e000289 (2020).
180. Yap, T. A. et al. Complex I inhibitor of oxidative phosphorylation in advanced solid tumors and acute myeloid leukemia: phase I trials. *Nat. Med.* **29**, 115–126 (2023).
181. Zachar, Z. et al. Non-redox-active lipoate derivates disrupt cancer cell mitochondrial metabolism and are potent anticancer agents in vivo. *J. Mol. Med.* **89**, 1137–1148 (2011).
182. Elia, I. et al. Tumor cells dictate anti-tumor immune responses by altering pyruvate utilization and succinate signaling in CD8+ T cells. *Cell Metab.* **34**, 1137–1150.e6 (2022).
183. Pardee, T. S. et al. A phase I study of the first-in-class antimitochondrial metabolism agent, CPI-613, in patients with advanced hematologic malignancies. *Clin. Cancer Res.* **20**, 5255–5264 (2014).
184. Peace, C. G., O'Carroll, S. M. & O'Neill, L. A. J. Fumarate hydratase as a metabolic regulator of immunity. *Trends Cell Biol.* **34**, 442–450 (2023).
185. Cheng, J. et al. Cancer-cell-derived fumarate suppresses the anti-tumor capacity of CD8+ T cells in the tumor microenvironment. *Cell Metab.* **35**, 961–978.e10 (2023).
186. Selak, M. A. et al. Succinate links TCA cycle dysfunction to oncogenesis by inhibiting HIF-α prolyl hydroxylase. *Cancer Cell* **7**, 77–85 (2005).
187. Tannahill, G. M. et al. Succinate is an inflammatory signal that induces IL-1β through HIF-1α. *Nature* **496**, 238–242 (2013).
188. Wu, J. Y. et al. Cancer-derived succinate promotes macrophage polarization and cancer metastasis via succinate receptor. *Mol. Cell* **77**, 213–227.e5 (2020).
189. Zitvogel, L., Ma, Y., Raoult, D., Kroemer, G. & Gajewski, T. F. The microbiome in cancer immunotherapy: diagnostic tools and therapeutic strategies. *Science* **359**, 1366–1370 (2018).
190. Björk, J. R. et al. Longitudinal gut microbiome changes in immune checkpoint blockade-treated advanced melanoma. *Nat. Med.* **30**, 785–796 (2024).
191. Steed, A. L. et al. The microbial metabolite desaminotyrosine protects from influenza through type I interferon. *Science* **357**, 498–502 (2017).
192. Joachim, L. et al. The microbial metabolite desaminotyrosine enhances T-cell priming and cancer immunotherapy with immune checkpoint inhibitors. *EBioMedicine* **97**, 104834 (2023).
193. Mirji, G. et al. The microbiome-derived metabolite TMAO drives immune activation and boosts responses to immune checkpoint blockade in pancreatic cancer. *Sci. Immunol.* **7**, eabn0704 (2022).
194. Tintelnot, J. et al. Microbiota-derived 3-IAA influences chemotherapy efficacy in pancreatic cancer. *Nature* **615**, 168–174 (2023).
195. Bender, M. J. et al. Dietary tryptophan metabolite released by intratumoral Lactobacillus reuteri facilitates immune checkpoint inhibitor treatment. *Cell* **186**, 1846–1862.e26 (2023).
196. Jia, D. et al. Microbial metabolite enhances immunotherapy efficacy by modulating T cell stemness in pan-cancer. *Cell* **187**, 1651–1665.e21 (2024).
197. Guo, H. et al. Multi-omics analyses of radiation survivors identify radioprotective microbes and metabolites. *Science* **370**, eaay9097 (2020).
198. Režen, T. et al. The role of bile acids in carcinogenesis. *Cell. Mol. Life Sci.* **79**, 243 (2022).
199. Ma, C. et al. Gut microbiome–mediated bile acid metabolism regulates liver cancer via NKT cells. *Science* **360**, eaan5931 (2018).
200. Hang, S. et al. Bile acid metabolites control T_H17 and T_{reg} cell differentiation. *Nature* **576**, 143–148 (2019).
201. Fidelle, M. et al. A microbiota-modulated checkpoint directs immunosuppressive intestinal T cells into cancers. *Science* **380**, eabo2296 (2023).
202. Lindner, S. et al. Altered microbial bile acid metabolism exacerbates T cell-driven inflammation during graft-versus-host disease. *Nat. Microbiol.* **9**, 614–630 (2024).
203. Ruutu, T. et al. Improved survival with ursodeoxycholic acid prophylaxis in allogeneic stem cell transplantation: long-term follow-up of a randomized study. *Biol. Blood Marrow Transpl.* **20**, 135–138 (2014).
204. Byrd, D. A. et al. Circulating bile acids and adenoma recurrence in the context of adherence to a high-fiber, high-fruit and vegetable, and low-fat dietary intervention. *Clin. Transl. Gastroenterol.* **13**, e00533 (2022).
205. Golonko, A. et al. Dietary factors and their influence on immunotherapy strategies in oncology: a comprehensive review. *Cell Death Dis.* **15**, 254 (2024).
206. Eriau, E., Paillet, J., Kroemer, G. & Pol, J. G. Metabolic reprogramming by reduced calorie intake or pharmacological caloric restriction mimetics for improved cancer immunotherapy. *Cancers* **13**, 1260 (2021).
207. Zitvogel, L., Derosa, L. & Kroemer, G. Modulation of cancer immunotherapy by dietary fibers and over-the-counter probiotics. *Cell Metab.* **34**, 350–352 (2022).
208. Smith, P. M. et al. The microbial metabolites, short-chain fatty acids, regulate colonic T reg cell homeostasis. *Science* **341**, 569–573 (2013).
209. Arpaia, N. et al. Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. *Nature* **504**, 451–455 (2013).
210. Furusawa, Y. et al. Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. *Nature* **504**, 446–450 (2013).
211. Coutzac, C. et al. Systemic short chain fatty acids limit antitumor effect of CTLA-4 blockade in hosts with cancer. *Nat. Commun.* **11**, 2168 (2020).
212. Nomura, M. et al. Association of short-chain fatty acids in the gut microbiome with clinical response to treatment with nivolumab or pembrolizumab in patients with solid cancer tumors. *JAMA Netw. Open.* **3**, e202895 (2020).
213. Spencer, C. N. et al. Dietary fiber and probiotics influence the gut microbiome and melanoma immunotherapy response. *Science* **374**, 1632–1640 (2021).
214. Gill, P. A., Muir, J. G., Gibson, P. R. & Van Zelm, M. C. A randomized dietary intervention to increase colonic and peripheral blood SCFAs modulates the blood B- and T-cell compartments in healthy humans. *Am. J. Clin. Nutr.* **116**, 1354 (2022).
215. Farias, R. et al. The DIET study: a randomized controlled trial of a high fiber diet in cancer patients (pts) receiving immune checkpoint blockade (ICB). *J. Clin. Oncol.* **41** (suppl. 16), Abstr. TPS9609 (2023).
216. Luu, M. et al. Microbial short-chain fatty acids modulate CD8+ T cell responses and improve adoptive immunotherapy for cancer. *Nat. Commun.* **12**, 4077 (2021).
217. Qiu, J. et al. Acetate promotes T cell effector function during glucose restriction. *Cell Rep.* **27**, 2063–2074.e5 (2019).
218. Peng, M. et al. Aerobic glycolysis promotes T helper 1 cell differentiation through an epigenetic mechanism. *Science* **354**, 481–484 (2016).
219. Balmer, M. L. et al. Memory CD8+ T cells require increased concentrations of acetate induced by stress for optimal function. *Immunity* **44**, 1312–1324 (2016).
220. Miller, K. D. et al. Acetate acts as a metabolic immunomodulator by bolstering T-cell effector function and potentiating antitumor immunity in breast cancer. *Nat. Cancer* **4**, 1491–1507 (2023).
221. Montégut, L., de Cabo, R., Zitvogel, L. & Kroemer, G. Science-driven nutritional interventions for the prevention and treatment of cancer. *Cancer Discov.* **12**, 2258–2279 (2022).
222. Luda, K. M. et al. Ketolysis drives CD8+ T cell effector function through effects on histone acetylation. *Immunity* **56**, 2021–2035.e8 (2023).
223. Cortellino, S. et al. Fasting mimicking diet in mice delays cancer growth and reduces immunotherapy-associated cardiovascular and systemic side effects. *Nat. Commun.* **14**, 5529 (2023).
224. Ferrere, G. et al. Ketogenic diet and ketone bodies enhance the anticancer effects of PD-1 blockade. *JCI Insight* **6**, e145207 (2021).
225. Klement, R. J. et al. Impact of a ketogenic diet intervention during radiotherapy on body composition: III - final results of the KETOCOMP study for breast cancer patients. *Breast Cancer Res.* **22**, 94 (2020).
226. Khodabakhshi, A. et al. Effects of ketogenic metabolic therapy on patients with breast cancer: a randomized controlled clinical trial. *Clin. Nutr.* **40**, 751–758 (2021).
227. Su, Z., Liu, Y., Xia, Z., Rustgi, A. K. & Gu, W. An unexpected role for the ketogenic diet in triggering tumor metastasis by modulating BACH1-mediated transcription. *Sci. Adv.* **10**, eadm9481 (2024).
228. Denk, D. et al. Expansion of T memory stem cells with superior anti-tumor immunity by urolithin A-induced mitophagy. *Immunity* **55**, 2059–2073.e8 (2022).
229. Messaoudene, M. et al. A natural polyphenol exerts antitumor activity and circumvents anti–PD-1 resistance through effects on the gut microbiota. *Cancer Discov.* **12**, 1070–1087 (2022).
230. Denk, D. et al. Impact of urolithin A supplementation, a mitophagy activator on mitochondrial health of immune cells (MitoIMMUNE): a randomized, double-blind, placebo-controlled trial in healthy adults. *J. Clin. Oncol.* **42** (suppl. 16), Abstr. e14562 (2024).
231. Trung, L. Q. & An, D. T. T. Is resveratrol a cancer immunomodulatory molecule? *Front. Pharmacol.* **9**, 1255 (2018).
232. Cai, H. et al. Cancer chemoprevention: evidence of a nonlinear dose response for the protective effects of resveratrol in humans and mice. *Sci. Transl. Med.* **7**, 298ra117 (2015).
233. Hofer, S. J. et al. Mechanisms of spermidine-induced autophagy and geroprotection. *Nat. Aging* **2**, 1112–1129 (2022).
234. Pietrocola, F. et al. Caloric restriction mimetics enhance anticancer immunosurveillance. *Cancer Cell* **30**, 147–160 (2016).
235. Hofer, S. J. et al. Spermidine is essential for fasting-mediated autophagy and longevity. *Nat. Cell Biol.* **26**, 1571–1584 (2024).
236. Zhang, H. et al. Polyamines control eIF5A hypusination, TFEB translation, and autophagy to reverse B cell senescence. *Mol. Cell* **76**, 110–125.e9 (2019).
237. Puleston, D. J. et al. Autophagy is a critical regulator of memory $CD8^+$ T cell formation. *eLife* **3**, e03706 (2014).
238. Lévesque, S. et al. A synergistic triad of chemotherapy, immune checkpoint inhibitors, and caloric restriction mimetics eradicates tumors in mice. *Oncoimmunology* **8**, e1657375 (2019).
239. Pietrocola, F. et al. Spermidine induces autophagy by inhibiting the acetyltransferase EP300. *Cell Death Differ.* **22**, 509–516 (2014).
240. Al-Habsi, M. et al. Spermidine activates mitochondrial trifunctional protein and improves antitumor immunity in mice. *Science* **378**, eabj3510 (2022).
241. Keohane, P. et al. Supplementation of spermidine at 40 mg/day has minimal effects on circulating polyamines: an exploratory double-blind randomized controlled trial in older men. *Nutr. Res.* **132**, 1–14 (2024).
242. Allen, N. C. et al. Nicotinamide for skin-cancer chemoprevention in transplant recipients. *N. Engl. J. Med.* **388**, 804–812 (2023).

243. Selvanesan, B. C. et al. Nicotinamide combined with gemcitabine is an immunomodulatory therapy that restrains pancreatic cancer in mice. *J. Immunother. Cancer* **8**, e001250 (2020).
244. Buqué, A. et al. Immunoprophylactic and immunotherapeutic control of hormone receptor-positive breast cancer. *Nat. Commun.* **11**, 3819 (2020).
245. Cichocki, F. et al. Nicotinamide enhances natural killer cell function and yields remissions in patients with non-Hodgkin lymphoma. *Sci. Transl. Med.* **15**, eade3341 (2023).
246. St. Paul, M. et al. Coenzyme A fuels T cell anti-tumor immunity. *Cell Metab.* **33**, 2415–2427.e6 (2021).
247. Bargiela, D. et al. Vitamin B6 metabolism determines T cell anti-tumor responses. *Front. Immunol.* **13**, 837669 (2022).
248. Kovatcheva, M. et al. Vitamin B12 is a limiting factor for induced cellular plasticity and tissue repair. *Nat. Metab.* **5**, 1911–1930 (2023).
249. Turgeman, I. et al. Too much of a good thing: the association of elevated vitamin B12 levels and outcomes in patients with cancer treated with immunotherapy. *J. Immunother.* **47**, 117–122 (2024).
250. Van de Roovaart, H. J. et al. Safety and efficacy of vitamin B in cancer treatments: a systematic review. *J. Oncol. Pharm. Pract.* **30**, 451–463 (2024).
251. Zhang, Y. G. et al. Vitamin D receptor protects against dysbiosis and tumorigenesis via the JAK/STAT pathway in intestine. *Cell Mol. Gastroenterol. Hepatol.* **10**, 729–746 (2020).
252. Giampazolias, E. et al. Vitamin D regulates microbiome-dependent cancer immunity. *Science* **384**, 428–437 (2024).
253. Vaughan-Shaw, P. G. et al. The impact of vitamin D pathway genetic variation and circulating 25-hydroxyvitamin D on cancer outcome: systematic review and meta-analysis. *Br. J. Cancer* **116**, 1092–1110 (2017).
254. Neale, R. E. et al. The D-health trial: a randomised controlled trial of the effect of vitamin D on mortality. *Lancet Diabetes Endocrinol.* **10**, 120–128 (2022).
255. Chandler, P. D. et al. Effect of vitamin D3 supplements on development of advanced cancer: a secondary analysis of the VITAL randomized clinical trial. *JAMA Netw. Open* **3**, e2025850 (2020).
256. Bersanelli, M. et al. Systematic vitamin D supplementation is associated with improved outcomes and reduced thyroid adverse events in patients with cancer treated with immune checkpoint inhibitors: results from the prospective PROVIDENCE study. *Cancer Immunol. Immunother.* **72**, 3707–3716 (2023).
257. Johnson, T. S. et al. Indoximod-based chemo-immunotherapy for pediatric brain tumors: a first-in-children phase I trial. *Neuro Oncol.* **26**, 348–361 (2024).
258. Jha, G. G. et al. A phase II randomized, double-blind study of sipuleucel-T followed by IDO pathway inhibitor, indoximod, or placebo in the treatment of patients with metastatic castration resistant prostate cancer (mCRPC). *Lancet Oncol.* **35**, 3066 (2017).
259. Chow, A., Perica, K., Klebanoff, C. A. & Wolchok, J. D. Clinical implications of T cell exhaustion for cancer immunotherapy. *Nat. Rev. Clin. Oncol.* **19**, 775–790 (2022).
260. Murphy, K., Weaver, C. *Janeway's Immunobiology, 9th edn* (Garland Science/Taylor & Francis, 2017).
261. Reina-Campos, M., Scharping, N. E. & Goldrath, A. W. CD8+ T cell metabolism in infection and cancer. *Nat. Rev. Immunol.* **21**, 718–738 (2021).
262. Wang, H. et al. CD36-mediated metabolic adaptation supports regulatory T cell survival and function in tumors. *Nat. Immunol.* **21**, 298–308 (2020).
263. Franco, F., Jaccard, A., Romero, P., Yu, Y. R. & Ho, P. C. Metabolic and epigenetic regulation of T-cell exhaustion. *Nat. Metab.* **2**, 1001–1012 (2020).
264. Wang, D. & DuBois, R. N. Eicosanoids and cancer. *Nat. Rev. Cancer* **10**, 181–193 (2010).
265. Harris, R. E. Cyclooxygenase-2 (cox-2) blockade in the chemoprevention of cancers of the colon, breast, prostate, and lung. *Inflammopharmacology* **17**, 55–67 (2009).
266. Bayerl, F. et al. Tumor-derived prostaglandin E2 programs cDC1 dysfunction to impair intratumoral orchestration of anti-cancer T cell responses. *Immunity* **56**, 1341–1358.e11 (2023).
267. Lacher, S. B. et al. PGE2 limits effector expansion of tumour-infiltrating stem-like CD8+ T cells. *Nature* **629**, 417–425 (2024).
268. Hennequart, M. et al. Constitutive IDO1 expression in human tumors is driven by cyclooxygenase-2 and mediates intrinsic immune resistance. *Cancer Immunol. Res.* **5**, 695–709 (2017).
269. Wang, S. J. et al. Effect of cyclo-oxygenase inhibitor use during checkpoint blockade immunotherapy in patients with metastatic melanoma and non-small cell lung cancer. *J. Immunother. Cancer* **8**, 889 (2020).
270. Zhang, Y. et al. Adding cyclooxygenase inhibitors to immune checkpoint inhibitors did not improve outcomes in metastatic renal cell carcinoma. *Cells* **11**, 2505 (2022).
271. Burn, J. et al. Cancer prevention with aspirin in hereditary colorectal cancer (Lynch syndrome), 10-year follow-up and registry-based 20-year data in the CAPP2 study: a double-blind, randomised, placebo-controlled trial. *Lancet* **395**, 1855–1863 (2020).
272. Elwood, P. et al. Aspirin and cancer treatment: systematic reviews and meta-analyses of evidence: for and against. *Br. J. Cancer* **130**, 3–8 (2024).
273. Foretz, M., Guigas, B. & Viollet, B. Metformin: update on mechanisms of action and repurposing potential. *Nat. Rev. Endocrinol.* **19**, 460–476 (2023).
274. Ma, R., Yi, B., Riker, A. I. & Xi, Y. Metformin and cancer immunity. *Acta Pharmacol. Sin.* **41**, 1403–1409 (2020).
275. Petakh, P., Kamyshna, I. & Kamyshnyi, A. Effects of metformin on the gut microbiota: a systematic review. *Mol. Metab.* **77**, 101805 (2023).
276. Afzal, M. Z., Mercado, R. R. & Shirai, K. Efficacy of metformin in combination with immune checkpoint inhibitors (anti-PD-1/anti-CTLA-4) in metastatic malignant melanoma. *J. Immunother. Cancer* **6**, 64 (2018).
277. Wang, S. et al. Low-dose metformin reprograms the tumor immune microenvironment in human esophageal cancer: results of a phase II clinical trial. *Clin. Cancer Res.* **26**, 4921–4932 (2020).
278. Augustin, R. C. et al. Metformin is associated with improved clinical outcomes in patients with melanoma: a retrospective, multi-institutional study. *Front. Oncol.* **13**, 1075823 (2023).
279. Akce, M. et al. Phase II trial of nivolumab and metformin in patients with treatment-refractory microsatellite stable metastatic colorectal cancer. *J. Immunother. Cancer* **11**, 7235 (2023).
280. Kordes, S. et al. Metformin in patients with advanced pancreatic cancer: a double-blind, randomised, placebo-controlled phase 2 trial. *Lancet Oncol.* **16**, 839–847 (2015).
281. Goodwin, P. J. et al. Effect of metformin vs placebo on invasive disease–free survival in patients with breast cancer: the MA.32 randomized clinical trial. *JAMA* **327**, 1963–1973 (2022).
282. Cuyàs, E. et al. The C allele of ATM rs11212617 associates with higher pathological complete remission rate in breast cancer patients treated with neoadjuvant metformin. *Front. Oncol.* **9**, 443988 (2019).

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Author contributions

The authors contributed equally to all aspects of the article.

Competing interests

S.K. has received honoraria from Cymab, Plectonic, TCR2 Inc., Miltenyi, Galapagos, Novartis, BMS and GSK. S.K. is an inventor of several patents in the field of immuno-oncology. S.K. received licence fees from TCR2 Inc. and Carina Biotech. S.K. received research support from TCR2 Inc., Tabby Therapeutics, Catalym GmBH, Plectonic GmBH and Arcus Bioscience for work unrelated to the article. G.K. has held research contracts with Daiichi Sankyo, Eleor, Kaleido, Lytix Pharma, PharmaMar, Osasuna Therapeutics, Samsara Therapeutics, Sanofi, Sutro, Tollys and Vascage. G.K. is on the Board of Directors of the Bristol Myers Squibb Foundation France. G.K. is a scientific co-founder of everImmune, Osasuna Therapeutics, Samsara Therapeutics and Therafast Bio. G.K. is on the scientific advisory boards of Hevolution, Institut Servier, Longevity Vision Funds and Rejuveron Life Sciences. G.K. is the inventor of patents covering therapeutic targeting of ageing, cancer, cystic fibrosis and metabolic disorders. L.Z. has held research contracts with GSK, Incyte, Lytix, Kaleido, Innovate Pharma, Daiichi Sankyo, Pilege, Merus, Transgene, 9m, Tusk and Roche, was on the on the Board of Directors of Transgene, is a co-founder of everImmune and holds patents covering the treatment of cancer and the therapeutic manipulation of the microbiota. G.K.'s brother, R. Kroemer, was an employee of Sanofi and now consults for Boehringer-Ingelheim. M.P.T. declares no competing interests.

Additional information

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