

REVIEW

Editorial Process: Submission:10/09/2024 Acceptance:11/18/2025 Published:11/20/2025

Immunometabolism in the Tumor Microenvironment: Dual Role in Modulating Anti-Tumor Immunity and Tumor Progression

Casterland Marbaniang*, Lakhon Kma, Rajeshwar Nath Sharan

Abstract

Understanding the tumor microenvironment (TME) requires a comprehensive exploration of the interactions between tumor cells and various stromal and immune cells, as these interactions significantly influence tumor growth and treatment response. Immunometabolism, which examines the relationship between immune cell metabolic processes and their behaviour, has become crucial in determining the effectiveness of anti-tumor immune responses. This review explores the intricate relationship between immunometabolism and TME, highlighting how metabolic changes in immune cells can either enhance or impair their capacity to fight cancer. It specifically investigates the metabolic reprogramming of T cells, macrophages, and dendritic cells within the TME and how these alterations affect their anti-tumor roles. The review also examines how tumors utilise metabolic pathways to establish an immunosuppressive environment that fosters tumor growth. Understanding these processes reveals potential therapeutic targets in immunometabolism to improve cancer treatment outcomes. By emphasising the dual role of immunometabolism in both aiding and inhibiting the immune response to cancer, this review underscores the necessity of integrating metabolic strategies into cancer immunotherapy research, which may lead to novel treatments that maximise the immune system's ability to combat cancer.

Keywords: Immunometabolism- TME, immune cells- tumor- immunosuppressive environment

Asian Pac J Cancer Prev, 26 (11), 3881-3893

Introduction

Immunometabolism explores how metabolic pathways regulate immune cell function, differentiation, and responses [1]. It has gained prominence in cancer research due to the critical interplay between immune cells and the tumor microenvironment (TME) [2]. This field connects metabolism with immunology, focusing on how metabolic shifts influence immune behaviour and activity [3]. Immune cells require metabolic reprogramming to support functions like defence, inflammation, and homeostasis [1,4]. In cancer, the rapid growth of tumor cells creates a nutrient-depleted, hypoxic TME that hinders immune cell activity, particularly T cells [5]. Tumor cells often outcompete immune cells for key nutrients such as glucose and amino acids, limiting effective antitumor responses [6]. Meanwhile, immune cells themselves depend on metabolic adaptation for activation and effector functions [7].

The TME consists of cancer cells, immune and stromal cells, vasculature, extracellular matrix (ECM), and signalling molecules as illustrated in Figure 1 [8]. These components interact intricately to promote tumor growth,

immune escape, and metastasis [9]. Metabolically, the TME is harsh characterised by hypoxia, nutrient scarcity, and acidosis which suppresses immune activity [10]. Hypoxia, for example, stabilises hypoxia-inducible factors (HIFs) that promote glycolysis and angiogenesis [11]. In addition, cancer cells' metabolic demands deplete glucose and amino acids, impairing immune effectors like T cells and macrophages [12]. Accumulation of lactate and other metabolic by-products also suppresses immune function and favours immunosuppressive cells like regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) [13]. Understanding immunometabolism in the TME is key to developing therapies that restore immune function and improve cancer outcomes. This review explores how metabolic reprogramming of immune cells within the TME can either promote or suppress anti-tumor immunity, offering insights into potential therapeutic targets.

The Role of Immunometabolism in Modulating Anti-Tumor Immunity

Tumor immunosurveillance refers to the dynamic process through which the immune system identifies and

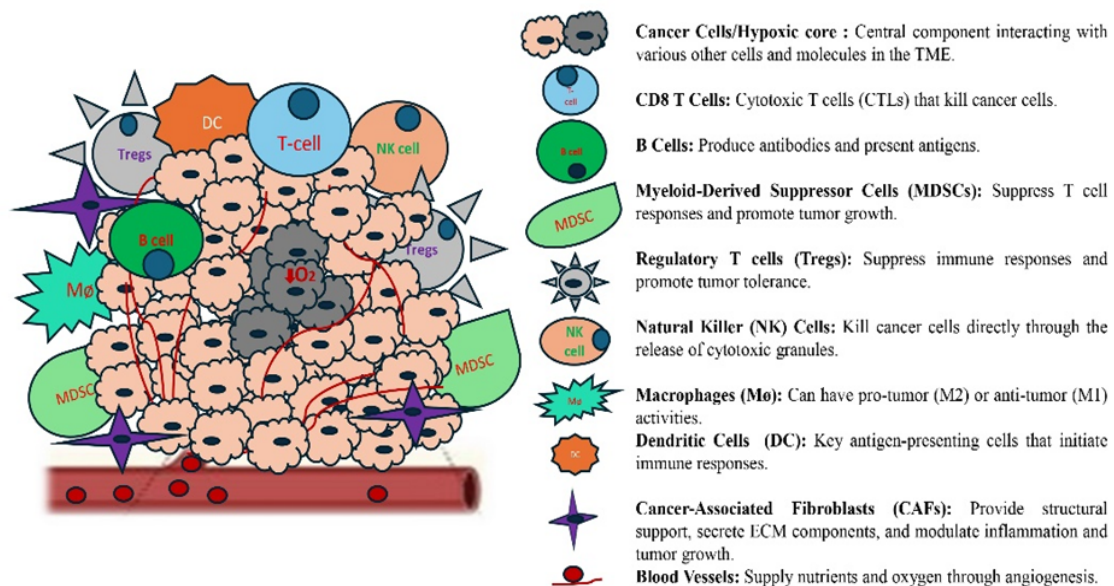


Figure 1. Major Cellular Components of the Tumour Microenvironment (TME). Some non-cellular components, such as cytokines, growth factors, extracellular matrix proteins, and metabolites, are not shown for simplicity.

eliminates cancer cells to prevent tumor development and progression [14]. This defence mechanism is orchestrated by specialised immune cells, notably cytotoxic T lymphocytes (CTLs), natural killer (NK) cells, and antigen-presenting cells (APCs) such as dendritic cells (DCs), as illustrated in Figure 2 [15, 16]. When neoplastic transformation occurs, cancer cells express abnormal or mutated self-antigens that are recognised by the immune system [17]. These tumor antigens are presented by APCs through Major Histocompatibility Complex (MHC) molecules MHC class I to CD8+ T cells and MHC class II to CD4+ helper T cells [18, 19]. Effective T cell activation requires the recognition of the antigen-MHC complex by the T cell receptor (TCR), along with co-stimulatory signalling through molecules

such as CD28 on T cells and CD80/CD86 on APCs [19]. This activation is further strengthened by cytokines such as IL-2 and IL-12, which promote T-cell proliferation and functional maturation [20]. Once activated, CD8+ T cells undergo clonal expansion, producing a pool of CTLs and memory T cells capable of targeting tumor cells, as shown in Figure 2. These memory cells rely primarily on oxidative phosphorylation (OXPHOS) to meet their energy demands and ensure long-term persistence [21, 22]. Upon reencounter with their specific antigen, they rapidly mount effective responses against tumor cells [21]. CTLs exert their cytotoxic effects through the secretion of perforin and granzymes, where perforin forms membrane pores that facilitate granzyme entry and trigger apoptosis via caspase cascades [23, 24]. Additionally, CTLs can

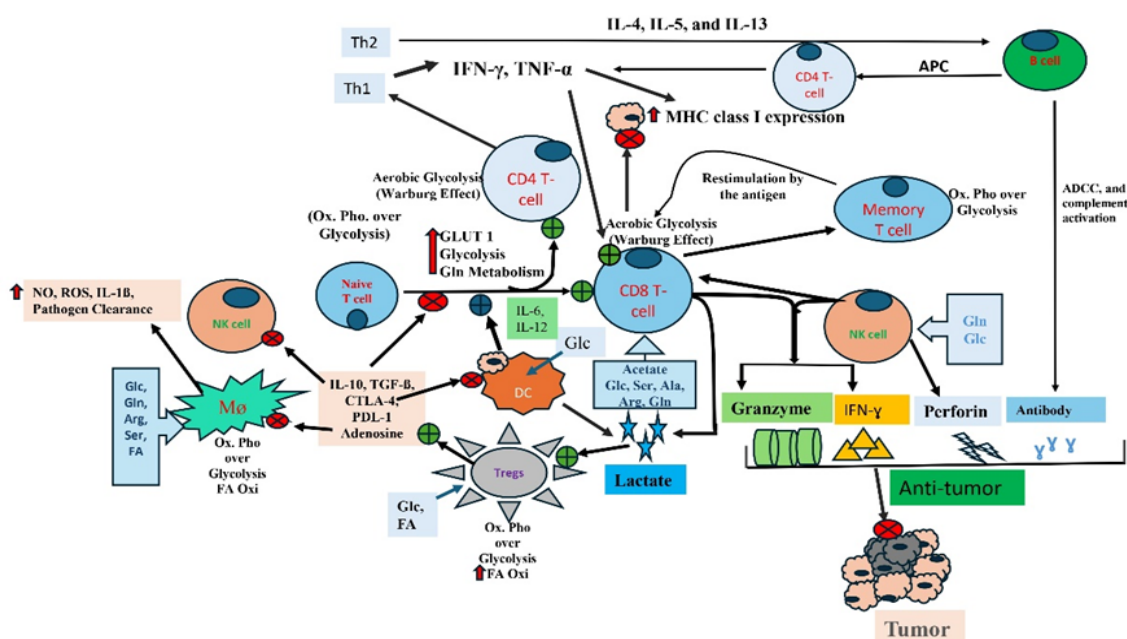


Figure 2. The Immune System's Role in Tumor Surveillance with Emphasis on Metabolic Pathways

initiate apoptosis through the Fas-FasL pathway, where FasL on CTLs binds to Fas receptors on tumor cells [25].

CD4⁺ T helper cells further enhance anti-tumor immunity by differentiating into subsets such as Th1 and Th2, as depicted in Figure 2 [26]. Th1 cells secrete IFN- γ and TNF- α , which potentiate immune responses by activating CD8⁺ T cells and other innate immune components [27]. IFN- γ upregulates MHC class I expression and enhances antigen presentation, while TNF- α boosts immune cell proliferation, damages tumor vasculature, and induces tumor apoptosis [28, 29]. TNF- α also increases MHC class I and II molecule expression, improving tumor recognition by the immune system [30, 31]. Th2 cells produce IL-4, IL-5, and IL-13, which aid in B cell activation and antibody production, particularly IgG and IgE [27]. These antibodies bind tumor antigens and initiate immune responses via antibody-dependent cellular cytotoxicity (ADCC) and complement activation, which involves NK cell-mediated killing and the formation of the membrane attack complex (MAC) [32]. In addition to antibody production, B cells can function as APCs and aid CD8⁺ T cell activation by providing necessary co-stimulatory signals and cytokines [33].

Metabolic reprogramming is vital for immune cell functionality, especially in the TME, where metabolic constraints are common [34]. Upon activation, T cells shift their metabolism from OXPHOS to aerobic glycolysis a process known as the Warburg effect to meet increased energetic and biosynthetic needs [35]. As shown in Figure 2, glucose becomes the principal fuel source, and its conversion to ATP via glycolysis provides essential intermediates for cell growth and cytokine production [36]. Enzymes like pyruvate kinase and hexokinase, along with glucose transporters such as GLUT1, drive this metabolic adaptation [36]. Beyond glucose, other metabolites play critical roles. Acetate supports histone acetylation and gene expression via acetyl-CoA; serine contributes one-carbon units for nucleotide synthesis; alanine supports glucose homeostasis; arginine enables nitric oxide (NO) production essential for T cell signalling; and glutamine provides carbon for the TCA cycle and nucleotide biosynthesis while countering oxidative stress [37–41]. These metabolic adaptations enable T cells to sustain anti-tumor responses despite the challenging TME.

Macrophages and dendritic cells also undergo metabolic reprogramming upon activation. Macrophages exhibit remarkable metabolic flexibility, allowing them to switch functions depending on environmental cues [1]. Pro-inflammatory M1 macrophages, which are involved in tumor surveillance and elimination, predominantly utilise glycolysis to generate ATP and intermediates necessary for producing inflammatory cytokines and mediating phagocytosis and cytotoxicity [1, 42]. On the other hand, M2 macrophages, associated with tissue repair and immune suppression, utilise FAO and OXPHOS, especially in the TME, where they promote angiogenesis and suppress immune responses [43, 44]. This metabolic reprogramming maintains the M2 phenotype and contributes to tumor growth. Thus, reprogramming macrophage metabolism toward an M1 phenotype may

enhance anti-tumor immunity [34]. Figure 2 shows that under physiological conditions, macrophages use glucose and fatty acids for functions like phagocytosis and cytokine production. Glycolysis supports inflammatory responses, while FAO supports tissue remodelling and inflammation resolution [4]. Arginase-1-mediated L-arginine metabolism plays a role in tissue repair and immunomodulation [45]. The TME alters the macrophage metabolic landscape low oxygen and nutrients drive macrophages to adopt glycolytic metabolism, favouring an M2-like phenotype [46]. Tumor-induced activation of arginase-1 and suppression of iNOS enhance L-arginine metabolism, promoting tumor progression and impairing anti-tumor immunity [47].

Dendritic cells (DCs), as depicted in Figure 2, are essential for linking innate and adaptive immunity through antigen capture, processing, and presentation to T cells [19, 48]. Upon activation by danger signals, DCs enhance glycolytic flux to meet energetic demands and support antigen presentation and cytokine production [4, 49]. DCs present antigens via MHC molecules and secrete IL-12 and IL-6 to guide T-cell differentiation [50]. They can also promote immune tolerance by presenting antigens in a non-inflammatory context to prevent autoimmunity [51]. Effective T cell activation relies on DC migration to lymph nodes, where they present processed antigens to naïve T cells [50]. However, in the TME, DCs often remain immature, with low expression of co-stimulatory molecules such as CD80 and CD86, impairing their ability to activate T cells [52]. Tumor-derived factors suppress DC maturation and function, while cytokines like IL-10 and TGF- β induce a tolerogenic DC phenotype that favours immune escape [53, 54]. Poor migration of DCs to lymph nodes and interaction with other suppressive cells like Tregs and MDSCs further diminishes their effectiveness in mounting anti-tumor immunity [55, 56].

As illustrated in Figure 2, NK cells play a central role in anti-tumor immunity through direct cytotoxicity, antibody-dependent cellular cytotoxicity (ADCC), cytokine release, and immune modulation [19]. They kill tumor cells by releasing perforin and granzymes and can bind to antibodies on tumor cells via Fc receptors to mediate ADCC [57]. NK cells secrete IFN- γ , enhancing CTL responses and antigen presentation, thus linking innate and adaptive immunity [58]. However, NK cell function is significantly impaired within the TME, where tumors produce immunosuppressive cytokines like TGF- β and IL-10, and express ligands for immune checkpoints such as Programmed Death-Ligand 1 (PD-L1) [59]. These factors reduce NK cell cytotoxicity and cytokine production [60]. Therapeutic strategies, including cytokine therapy, checkpoint blockade, and TME modulation, aim to restore NK cell activity for effective cancer treatment [61]. Tregs, a subset of CD4⁺ T cells, are essential for maintaining immune homeostasis and preventing autoimmunity by suppressing excessive immune responses [62]. These cells, marked by FoxP3 expression, utilise OXPHOS for energy to support long-term survival and suppressive function [63, 64]. Tregs maintain immune equilibrium by preventing prolonged immune activation and collateral tissue damage [62]. As

shown in Figure 2, Tregs suppress immune responses by secreting IL-10 and TGF- β , which inhibit the activation of T cells, macrophages, and DCs [65]. They can directly kill effector immune cells via granzyme and perforin-mediated cytotoxicity [66]. Tregs also deplete IL-2 from the environment, depriving other immune cells of this critical growth factor, and release adenosine and cyclic AMP to inhibit immune functions [67]. Additionally, Tregs modulate DC function by engaging LAG-3 with MHC class II and inducing IDO expression via Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4), which degrades tryptophan to suppress T cell activation [68, 69]. By keeping immune activation in check, Tregs prevent excessive responses that could lead to tissue damage and autoimmunity. Their role is vital in preserving the delicate balance of the immune system, ensuring it can distinguish between self and non-self, and preventing harmful attacks on the body's tissues [65].

The Dual Role of Immunometabolism in Tumor Progression

Understanding the complex interaction between cellular metabolism and the tumor microenvironment (TME) is essential, as metabolic alterations in both immune and cancer cells significantly influence tumor development and progression [2]. Figure 3 illustrates how these metabolic changes result in immunosuppression through multiple pathways [12]. This immunosuppressive environment favours tumor growth and compromises effective anti-tumor immune responses [70]. The TME orchestrates this suppressive milieu through several mechanisms involving various immune and stromal cell populations.

Macrophage Polarisation and Metabolism

As illustrated in Figure 3, Tumor-associated macrophages (TAMs) polarise toward an M2-like,

immunosuppressive phenotype under the influence of hypoxia, nutrient deprivation, and high lactate levels in the TME [71]. Hypoxia activates transcriptional programs via hypoxia-inducible factors (HIFs), which promote vascular endothelial growth factor (VEGF) expression, facilitating angiogenesis and the recruitment and polarisation of macrophages into TAMs [72]. Genes such as Arginase 1 (ARG1), CD206 (mannose receptor), and IL-10 are upregulated in this process, enhancing the anti-inflammatory and immunosuppressive characteristics of TAMs [46, 73, 74]. Other hypoxia-driven factors, such as TGF- β and CXCL12 (SDF-1, Stromal-Derived Factor-1), contribute to further recruitment and polarisation of macrophages [73, 75]. CCL2 (MCP-1, Monocyte Chemoattractant Protein-1) plays an additional role in attracting monocytes to the tumor site, where they differentiate into M2-like TAMs [76]. Elevated lactate levels, a byproduct of aerobic glycolysis (Warburg effect), enhance the production of IL-10 and TGF- β , further suppressing T-cell function [77]. Nutrient deprivation within the TME forces TAMs to rely on lipid metabolism, which reinforces their pro-tumorigenic and immunosuppressive activities [78]. TAMs also secrete matrix metalloproteinases (MMPs) and growth factors that support tumor invasion and progression [79]. Moreover, TAMs express immune checkpoint molecules like PD-L1, which, by binding to PD-1 on T cells, facilitates immune evasion [80]. These collective features reinforce TAM-mediated immunosuppression, contributing to tumor progression and resistance to therapy.

Myeloid-Derived Suppressor Cells (MDSCs)

MDSCs are heterogeneous populations of immature myeloid cells that suppress immune responses and are expanded in pathological conditions like cancer [81].

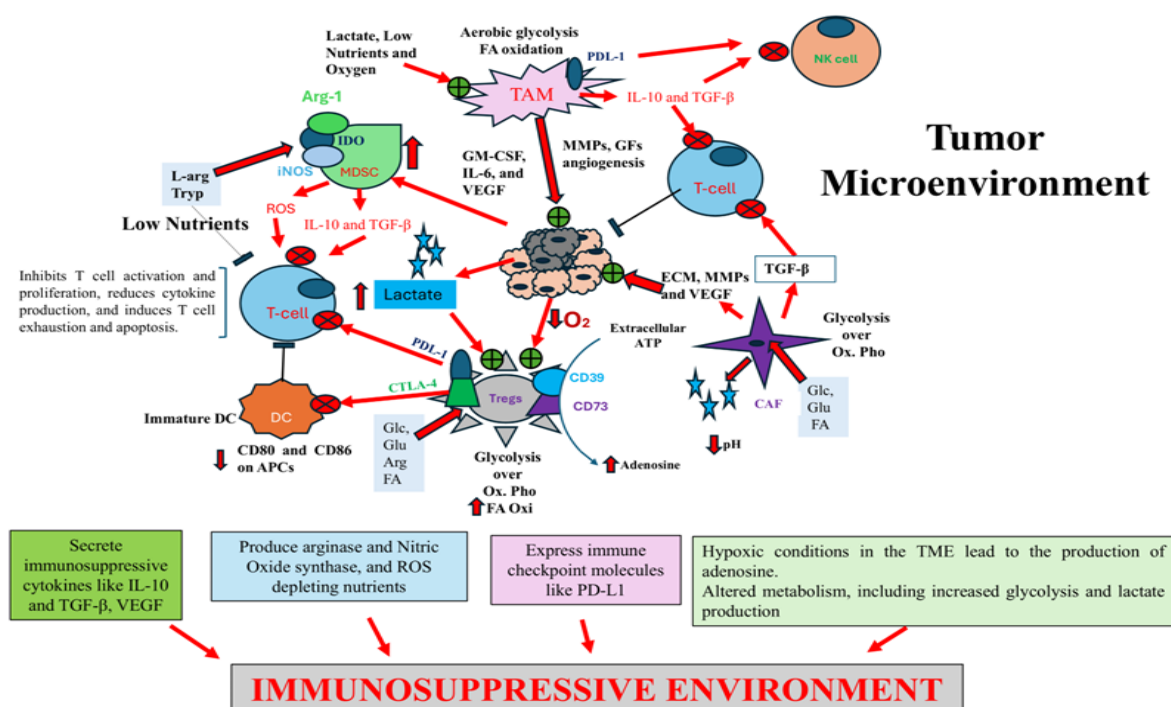


Figure 3. Immune Evasion through Immunosuppressive Mechanisms and Metabolic Alterations in the TME.

Under homeostatic conditions, MDSCs are rare, but in the TME, their numbers rapidly increase in response to stress, inflammation, and tumor-derived signals [81]. They prevent excessive immune activation and maintain homeostasis but are co-opted by tumors to suppress anti-tumor immunity [82]. Growth factors such as GM-CSF (Granulocyte-Macrophage Colony-Stimulating Factor), G-CSF (Granulocyte Colony-Stimulating Factor), and M-CSF (Macrophage Colony-Stimulating Factor), along with pro-inflammatory cytokines like IL-6, IL-10, and TNF- α , promote MDSC proliferation and immunosuppressive capacity [82-84]. S100A8/A9 proteins also support their recruitment and activation [85]. Activation of STAT3 (Signal Transducer and Activator of Transcription 3) and NF- κ B (Nuclear Factor kappa-light-chain-enhancer of activated B cells) signalling pathways in response to tumor-derived signals drives expression of ARG1, iNOS (Inducible Nitric Oxide Synthase), and COX-2 (Cyclooxygenase-2), key enzymes involved in MDSC-mediated suppression [82]. Figure 3 demonstrates that MDSCs inhibit T cells through multiple mechanisms, including IDO-mediated tryptophan catabolism into immunosuppressive kynurenine [86]. They also deplete L-arginine and cysteine via upregulation of arginase-1 and iNOS, and the resultant reactive oxygen species (ROS) further impair T-cell signalling [87]. MDSCs secrete IL-10 and TGF- β , promoting Treg differentiation and inhibiting dendritic cell (DC) maturation, thereby hampering antigen presentation and immune activation [82, 88]. They also modulate DC function via IL-10 and prostaglandin E2 (PGE2), secretion [82]. Additionally, MDSCs accumulate lactate and other metabolites that suppress effector immune functions [89]. Their ability to promote Treg expansion and sustain a suppressive environment within the TME positions MDSCs as critical targets for enhancing anti-tumor immunity [90, 91].

Regulatory T Cells (Tregs)

Tregs are crucial mediators of immune tolerance and are often co-opted by tumors to suppress anti-tumor immune responses, thereby facilitating tumor progression [92]. They secrete immunosuppressive cytokines such as IL-10 and TGF- β , which inhibit effector T cells and antigen-presenting cells [93]. Although Tregs rely on oxidative phosphorylation (OXPHOS) under homeostatic conditions, their metabolism adapts within the TME to support glycolysis under hypoxic conditions for ATP production and suppressive function [64, 94-96]. Tregs also utilise fatty acid oxidation (FAO) and lipid droplet formation to sustain their suppressive phenotype and support biosynthesis [67, 97]. Metabolites such as arginine and glutamine modulate Treg activity; arginase-1-mediated arginine breakdown and glutamine uptake promote Treg survival and suppressive capabilities [98, 99]. Lactate accumulation in the TME further enhances Treg function by upregulating immune checkpoint molecules such as PD-L1 and CTLA-4 [100-102]. Tregs express CD39 and CD73, which convert extracellular ATP into immunosuppressive adenosine, inhibiting effector T cell activity [103]. Additional checkpoints, including CTLA-4, PD-1, and LAG-3, function to inhibit

T cell activation through competitive ligand binding or inhibitory signalling [65, 104, 105]. These mechanisms enable Tregs to maintain a suppressive microenvironment, impairing effective anti-tumor immune responses as illustrated in Figure 3.

Cancer-Associated Fibroblasts (CAFs)

Fibroblasts, which normally support tissue structure by producing extracellular matrix (ECM) components such as collagen and elastin, are reprogrammed in the TME into CAFs that contribute to tumor progression [106]. In physiological states, fibroblasts use OXPHOS to generate ATP and regulate ECM remodelling and cytokine secretion to aid tissue repair [107]. However, CAFs in tumors display enhanced glycolysis and lactate secretion, which acidify the TME, impair immune cell function, and facilitate tumor invasion [108, 109]. These fibroblasts produce high levels of ECM components and remodelling enzymes like MMPs and collagen, creating a dense stroma conducive to tumor migration and metastasis [108]. CAFs also upregulate lipid and glutamine metabolism to fuel ECM remodelling and tumor support [109]. By secreting VEGF and TGF- β , CAFs promote angiogenesis and stromal remodelling [110, 111]. Additionally, they release factors that attract Tregs and MDSCs, amplifying local immunosuppression as illustrated in Figure 3 [112, 113]. These features underscore CAFs' role in shaping a TME that favours tumor immune evasion and therapeutic resistance [114].

Metabolic Competition and Nutrient Depletion

Cancer cells reprogram their metabolism to prioritise glycolysis, glutaminolysis, and lipogenesis, fostering an environment of intense nutrient competition [115]. This leads to a depletion of key substrates such as glucose, amino acids, and fatty acids, which impairs the effector functions of T cells and NK cells [116, 117]. Tryptophan and arginine, essential for T cell proliferation and activation, are metabolised by tumor cells and suppressive myeloid populations to induce immune suppression [118]. Upregulation of IDO by tumor and stromal cells catalyses the conversion of tryptophan into kynurenine, which inhibits T-cell responses and promotes Treg differentiation [119, 68]. Arginine metabolism by MDSCs and TAMs, via arginase, further depletes this critical nutrient, weakening TCR signalling and T cell expansion [87, 73]. Deficiency in these amino acids ultimately impairs anti-tumor immune responses and facilitates tumor survival and proliferation [120, 121]. Fatty acid metabolism also plays a key role in the TME. While tumor cells and suppressive immune cells like Tregs and MDSCs rely on FAO for energy, effector T cells predominantly depend on glycolysis, making them particularly vulnerable in nutrient-depleted conditions [122-124]. This metabolic asymmetry, as illustrated in Figure 3, creates a TME that strongly favours tumor progression over immune surveillance [5, 124].

Hypoxia and HIFs

Rapid tumor expansion outpaces angiogenesis, leading to hypoxic zones within the TME [125]. Under such conditions, HIF-1 α and HIF-2 α are stabilised

and function as transcriptional regulators of genes that promote adaptation to hypoxia, angiogenesis, and immune modulation [126]. HIFs enhance glucose uptake and lactate production to meet energetic demands despite oxygen availability, further promoting the Warburg effect [11]. VEGF expression is also induced by HIFs, which stimulate neovascularisation, though the resulting vasculature is often disorganised and leaky [127, 128]. Hypoxia-driven expression of PD-L1 on both tumor and immune cells diminishes T cell activation and contributes to T cell exhaustion [129, 130]. Moreover, hypoxia enhances the accumulation and suppressive function of Tregs and MDSCs, reinforcing immune evasion as illustrated in Figure 3 [131, 132].

Adenosine Accumulation

In hypoxic tumors, as illustrated in Figure 3, extracellular ATP is released and hydrolysed by CD39 and CD73 into adenosine [133]. Adenosine acts on A2A receptors in immune cells, resulting in the suppression of T cell and NK cell effector functions, including cytokine production and cytotoxicity [134, 135]. As mentioned earlier, adenosine also enhances the activity of Tregs and MDSCs, which suppress effector T cell responses and promote immune tolerance [103]. Understanding the adenosine-A2A receptor axis is crucial in comprehending how it contributes to the creation of an immunosuppressive TME, protecting tumors from immune destruction [135]. A study by Hatfield et al. [136] showed that combining PD-1 checkpoint inhibition with A2A receptor blockade significantly enhanced anti-tumor responses in mice. This combination reduced adenosine's immunosuppressive effects, increased T cell activity, and promoted tumor regression, highlighting the potential of targeting the adenosine pathway to enhance the effectiveness of existing immunotherapies in cancer treatment [136].

Lactate Production and Acidic Microenvironment

Lactate production is elevated in the TME due to enhanced glycolysis in both tumor and immune cells [137, 138]. LDH catalyses the conversion of pyruvate to lactate, fueling the acidic milieu [139]. As depicted in Figure 3, this acidification suppresses T cell receptor (TCR) signalling, reduces IFN- γ production, and impairs T and NK cell activity [140, 141]. Furthermore, lactate promotes Treg expansion and shifts macrophage polarisation toward the M2 phenotype, exacerbating immune suppression [71, 72]. This creates a feedback loop that maintains immune suppression and tumor progression. Inhibiting LDH has been shown to reduce lactate production and improve the efficacy of immune checkpoint blockade [13, 142].

The Balance Between Immunometabolism and Anti-Tumor Immunity

Achieving effective cancer control depends on maintaining a delicate balance between immunometabolism and anti-tumor immunity. Sustaining this equilibrium requires an understanding of how immune cell metabolism responds to suppressive and nutrient-deprived conditions within the TME. As established, the TME is characterised by hypoxia, acidosis, and nutrient scarcity, which

collectively impair the metabolic activity and function of immune effector cells while simultaneously supporting the metabolic reprogramming of tumor cells to evade the immune attack and drive tumor progression [115].

Targeting Metabolic Pathways

One of the central strategies to restore immune function is by targeting the metabolic pathways that cancer cells heavily rely upon. Tumor cells upregulate aerobic glycolysis (the Warburg effect) and glutaminolysis to sustain their rapid proliferation and biosynthetic needs [115, 143]. Targeting enzymes such as hexokinase 2 and glutaminase can reduce the metabolic fitness of tumor cells. For example, 3-bromopyruvate, a pyruvate analogue, inhibits glycolysis and has been shown to kill tumor cells effectively [144]. Inhibiting lactate dehydrogenase (LDH) reduces lactate production, thereby mitigating the immunosuppressive acidic microenvironment. LDH inhibitors have also been reported to restore T and natural killer (NK) cell functions [13]. Similarly, inhibition of indoleamine 2,3-dioxygenase (IDO), an enzyme responsible for catabolizing tryptophan into immunosuppressive kynurenine, using agents like indoximod has shown promise in reversing immune suppression in preclinical and early clinical studies [145, 146]. Additionally, adenosine accumulation in the hypoxic TME activates A2A receptors on immune cells and contributes to immunosuppression. Blocking A2A receptors has been demonstrated to enhance T cell and NK cell activity in tumor models [136, 147]. Histone deacetylase (HDAC) inhibitors like vorinostat can further modulate gene expression in immune cells, boosting their anti-tumor functions and showing efficacy in certain malignancies such as cutaneous T-cell lymphoma [148].

Modulating Nutrient Availability

Immune cells rely on nutrients such as arginine, glutamine, and glucose to maintain their effector functions, proliferation, and cytokine production [149]. However, within the TME, tumor cells compete with immune cells for these resources, often resulting in nutrient depletion and immune dysfunction [118]. Supplementation of specific amino acids may restore immune activity. Arginine supplementation, for example, has been shown to promote T cell survival and expansion, supporting stronger immune responses against tumors [150]. Glutamine, another key nutrient, enhances the function of activated immune cells, although care must be taken due to the potential for glutamine to also fuel tumor cell metabolism [151]. Efforts to modulate glucose availability through analogues like 2-deoxyglucose have demonstrated the ability to impair tumor glycolysis while preserving immune cell function, thereby favouring anti-tumor immunity [152].

Immune Checkpoint Inhibition

Immune checkpoint blockade is a transformative approach in cancer immunotherapy. The PD-1/PD-L1 axis is frequently exploited by tumor cells to inactivate T cells. Therapeutic antibodies such as pembrolizumab and nivolumab block this interaction and reinvigorate T-cell responses, and have shown significant efficacy in

cancers such as melanoma, non-small cell lung cancer (NSCLC), and bladder cancer [153–155]. Similarly, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) is another checkpoint that negatively regulates T-cell activation. The monoclonal antibody ipilimumab blocks CTLA-4 and enhances T-cell proliferation, showing success, particularly in metastatic melanoma [156, 157].

Adoptive Cell Therapy

Adoptive cell therapy (ACT) involves the ex vivo manipulation of immune cells to enhance their anti-tumor potential. Chimeric antigen receptor (CAR) T cell therapy modifies T cells to express synthetic receptors that target tumor-associated antigens, improving the recognition and destruction of cancer cells [158]. CAR-T cells have produced durable responses in hematologic malignancies such as acute lymphoblastic leukaemia (ALL) and diffuse large B-cell lymphoma (DLBCL) [159]. Another ACT strategy, tumor-infiltrating lymphocyte (TIL) therapy, involves harvesting lymphocytes from tumors, expanding them in vitro, and reinfusing them to boost immune responses [160]. This method has proven particularly effective in treating melanoma and is being explored in other solid tumors [161–163]. Despite its promise, challenges remain due to the suppressive TME and tumor antigen heterogeneity.

Cytokine Therapy

Cytokine therapy enhances immune cell proliferation and activation. Interleukin-2 (IL-2) is a key cytokine that promotes the expansion of CTLs and NK cells. High-dose IL-2 therapy has been effective in metastatic melanoma and renal cell carcinoma, eliciting durable clinical responses [164, 165]. Interferons such as IFN- α and IFN- β play additional roles by increasing antigen presentation, enhancing MHC expression, and promoting tumor apoptosis. IFN- α has been used successfully in the treatment of several cancers, including melanoma and renal cell carcinoma [166, 167].

Vaccine-Based Approaches

Therapeutic cancer vaccines aim to initiate targeted immune responses by presenting tumor-specific antigens. Sipuleucel-T, for instance, is an FDA-approved vaccine for prostate cancer that targets prostatic acid phosphatase (PAP) and has shown survival benefits [168]. Dendritic cell (DC)-based vaccines involve pulsing patient-derived DCs with tumor antigens ex vivo and reinfusing them to enhance T cell priming and activation. These vaccines aim to enhance immune surveillance and anti-tumor activity through improved antigen presentation [169].

Targeting Tumor Vasculature

Angiogenesis, driven largely by vascular endothelial growth factor (VEGF), supports tumor growth and immune evasion. Anti-angiogenic agents such as bevacizumab inhibit VEGF and normalise tumor vasculature, improving oxygenation and immune cell infiltration into the tumor [170]. This strategy has been shown to enhance the efficacy of chemotherapy and immunotherapy in cancers such as colorectal cancer and NSCLC [171]. Vascular

normalisation also alleviates hypoxia, thereby reducing HIF-induced immunosuppressive mechanisms [172].

Combining Metabolic and Immune Checkpoint Inhibitors

Combining metabolic inhibitors with immune checkpoint inhibitors (ICIs) offers a synergistic strategy to reverse immune suppression. For example, combining PD-1 blockade with CB-1158, an arginase inhibitor, has been shown to increase T-cell infiltration and anti-tumor activity in preclinical models [70, 173, 174]. Similarly, combining LDH inhibition with PD-1 blockade mitigates lactate accumulation and promotes T cell-mediated cytotoxicity [175]. Co-targeting IDO and CTLA-4 has also shown improved tumor control by restoring tryptophan availability and enhancing T-cell responses [175]. Further, combination strategies involving cancer vaccines and adoptive cell therapies such as CAR T cells have demonstrated improved antigen-specific responses and the potential to overcome tumor immune evasion [38, 176]. Despite these promising results, clinical optimization regarding dosing, scheduling, and patient selection remains necessary to minimize adverse effects and maximize therapeutic efficacy. In summary, rebalancing immunometabolism in the TME requires a multifaceted therapeutic approach. By correcting nutrient competition, targeting immunosuppressive enzymes and metabolites, and enhancing immune cell function through checkpoint blockade, vaccines, and cellular therapies, it is possible to overcome tumor-induced immune dysfunction and achieve more durable responses in cancer therapy.

Conclusion

The TME represents a complex and dynamic ecosystem where cancer cells and immune cells coexist in a metabolically hostile and immunosuppressive milieu. Within this environment, immunometabolism emerges as a critical determinant of immune cell fate, function, and anti-tumor efficacy. The reprogramming of metabolic pathways not only allows tumor cells to thrive under hypoxic and nutrient-depleted conditions but also actively impairs immune surveillance by altering the metabolic preferences and activities of key immune cell populations. Effector immune cells, including CTLs, DCs, and NK cells, require sufficient metabolic substrates such as glucose, amino acids, and fatty acids to execute their tumor-killing functions. However, the tumor's heightened metabolic demand often results in nutrient competition, leading to immune cell exhaustion and dysfunction. Conversely, regulatory immune cells such as MDSCs and regulatory T cells (Tregs) are better adapted to the metabolically stressed TME, further tipping the balance toward immune evasion and tumor progression. A nuanced understanding of these metabolic shifts has opened new avenues for therapeutic intervention. Targeting tumor-specific metabolic pathways, modulating nutrient availability, and inhibiting immunosuppressive metabolites such as lactate, adenosine, and kynurenine have demonstrated promising preclinical outcomes. Furthermore, the integration of metabolic inhibitors with immunotherapies, such as immune checkpoint blockade and adoptive cell transfer, offers a synergistic strategy to restore immune competence

and reshape the TME in favour of anti-tumor immunity. It is increasingly clear that immunometabolism serves as both a barrier and a lever in cancer immunotherapy. The dual role it plays—supporting immune cell function while also facilitating tumor-mediated immune suppression necessitates a careful, context-dependent therapeutic approach. Personalised interventions that consider tumor metabolic profiles, immune cell metabolic states, and patient-specific factors will likely be required to optimise treatment outcomes. As research continues to uncover the intricate connections between metabolism and immune regulation, future strategies must aim not only to inhibit tumor metabolism but also to empower immune cells metabolically. Such approaches hold great promise in shifting the balance within the TME toward durable and effective anti-tumor responses, thereby improving clinical outcomes for cancer patients.

Author Contribution Statement

Dr. Casterland Marbaniang conceptualized the review, conducted the literature search, analyzed and synthesized the data, and prepared the manuscript. Professor. Lakhon Kma and Retd. Professor. Rajeshwar Nath Sharan critically reviewed the manuscript and approved the final version for submission.

Acknowledgements

The authors gratefully acknowledge the Department of Biochemistry, North-Eastern Hill University (NEHU), Shillong, for providing the platform and support to carry out this study. The authors also sincerely thank the International Atomic Energy Agency (IAEA) for its support through the IAEA project.

Consent for Publication

This is not applicable, as this review article does not include any person's data.

Funding

This review was conducted without any specific grant from public, commercial, or not-for-profit funding agencies. However, the article processing charges (APC) will be covered by the International Atomic Energy Agency (IAEA) through the IAEA project.

Scientific Body Approval / Student Thesis Status

This review article is not part of any approved student thesis and was not submitted to any scientific body for approval.

Ethical Approval

As this is a review article based solely on published literature and does not involve any direct experiments with human or animal subjects, ethical approval was not required.

Availability of Data

No new datasets were generated or analyzed during this study. All data discussed are from publicly available

published articles.

Study Registration

As this is a narrative review article and not a clinical trial, meta-analysis, or guideline, it was not registered in any clinical or systematic review registry.

Conflict of Interest

The author declares no conflict of interest.

References

- O'Neill LA, Pearce EJ. Immunometabolism governs dendritic cell and macrophage function. *J Exp Med*. 2016;213(1):15-23. <https://doi.org/10.1084/jem.20151570>.
- Guo C, Chen S, Liu W, Ma Y, Li J, Fisher PB, et al. Immunometabolism: A new target for improving cancer immunotherapy. *Adv Cancer Res*. 2019;143:195-253. <https://doi.org/10.1016/bs.acr.2019.03.004>.
- Chavakis T. Immunometabolism: Where immunology and metabolism meet. *J Innate Immun*. 2022;14(1):1-3. <https://doi.org/10.1159/000521305>.
- Pearce EL, Pearce EJ. Metabolic pathways in immune cell activation and quiescence. *Immunity*. 2013;38(4):633-43. <https://doi.org/10.1016/j.immuni.2013.04.005>.
- Scharping NE, Delgoffe GM. Tumor microenvironment metabolism: A new checkpoint for anti-tumor immunity. *Vaccines (Basel)*. 2016;4(4). <https://doi.org/10.3390/vaccines4040046>.
- Wang T, Liu G, Wang R. The intercellular metabolic interplay between tumor and immune cells. *Front Immunol*. 2014;5:358. <https://doi.org/10.3389/fimmu.2014.00358>.
- Traba J, Sack MN, Waldmann TA, Anton OM. Immunometabolism at the nexus of cancer therapeutic efficacy and resistance. *Front Immunol*. 2021;12:657293. <https://doi.org/10.3389/fimmu.2021.657293>.
- Binnewies M, Roberts EW, Kersten K, Chan V, Fearon DF, Merad M, et al. Understanding the tumor immune microenvironment (time) for effective therapy. *Nat Med*. 2018;24(5):541-50. <https://doi.org/10.1038/s41591-018-0014-x>.
- Joyce JA, Fearon DT. T cell exclusion, immune privilege, and the tumor microenvironment. *Science*. 2015;348(6230):74-80. <https://doi.org/10.1126/science.aaa6204>.
- DeBerardinis RJ, Chandel NS. Fundamentals of cancer metabolism. *Sci Adv*. 2016;2(5):e1600200. <https://doi.org/10.1126/sciadv.1600200>.
- Marbaniang C, Kma L. Dysregulation of glucose metabolism by oncogenes and tumor suppressors in cancer cells. *Asian Pac J Cancer Prev*. 2018;19(9):2377-90. <https://doi.org/10.22034/apjcp.2018.19.9.2377>.
- Shi R, Tang YQ, Miao H. Metabolism in tumor microenvironment: Implications for cancer immunotherapy. *MedComm (2020)*. 2020;1(1):47-68. <https://doi.org/10.1002/mco2.6>.
- Li Z, Cui J. Targeting the lactic acid metabolic pathway for antitumor therapy. *Mol Ther Oncolytics*. 2023;31:100740. <https://doi.org/10.1016/j.omto.2023.100740>.
- Dunn GP, Bruce AT, Ikeda H, Old LJ, Schreiber RD. Cancer immunoediting: From immunosurveillance to tumor escape. *Nat Immunol*. 2002;3(11):991-8. <https://doi.org/10.1038/ni1102-991>.
- Dunn GP, Old LJ, Schreiber RD. The immunobiology of cancer immunosurveillance and immunoediting. *Immunity*. 2004;21(2):137-48. <https://doi.org/10.1016/j.immuni.2004.07.017>.

16. Vesely MD, Kershaw MH, Schreiber RD, Smyth MJ. Natural innate and adaptive immunity to cancer. *Annu Rev Immunol.* 2011;29:235-71. <https://doi.org/10.1146/annurev-immunol-031210-101324>.
17. Schumacher TN, Schreiber RD. Neoantigens in cancer immunotherapy. *Science.* 2015;348(6230):69-74. <https://doi.org/10.1126/science.aaa4971>.
18. Rock KL, Reits E, Neefjes J. Present yourself! By mhc class i and mhc class ii molecules. *Trends Immunol.* 2016;37(11):724-37. <https://doi.org/10.1016/j.it.2016.08.010>.
19. Janeway CA, Travers P, Walport M, Shlomchik MJ. *Immunobiology: The Immune System in Health and Disease.* 5th ed. Garland Science; 2001.
20. Smith-Garvin JE, Koretzky GA, Jordan MS. T cell activation. *Annu Rev Immunol.* 2009;27:591-619. <https://doi.org/10.1146/annurev.immunol.021908.132706>.
21. Wherry EJ, Kurachi M. Molecular and cellular insights into t cell exhaustion. *Nat Rev Immunol.* 2015;15(8):486-99. <https://doi.org/10.1038/nri3862>.
22. van der Leun AM, Thommen DS, Schumacher TN. Cd8(+) t cell states in human cancer: Insights from single-cell analysis. *Nat Rev Cancer.* 2020;20(4):218-32. <https://doi.org/10.1038/s41568-019-0235-4>.
23. Xie Q, Ding J, Chen Y. Role of cd8(+) t lymphocyte cells: Interplay with stromal cells in tumor microenvironment. *Acta Pharm Sin B.* 2021;11(6):1365-78. <https://doi.org/10.1016/j.apsb.2021.03.027>.
24. Voskoboinik I, Whisstock JC, Trapani JA. Perforin and granzymes: Function, dysfunction and human pathology. *Nat Rev Immunol.* 2015;15(6):388-400. <https://doi.org/10.1038/nri3839>.
25. Waring P, Müllbacher A. Cell death induced by the fas/fas ligand pathway and its role in pathology. *Immunol Cell Biol.* 1999;77(4):312-7. <https://doi.org/10.1046/j.1440-1711.1999.00837.x>.
26. Zhu J, Paul WE. Cd4 t cells: Fates, functions, and faults. *Blood.* 2008;112(5):1557-69. <https://doi.org/10.1182/blood-2008-05-078154>.
27. Romagnani S. Th1/th2 cells. *Inflamm Bowel Dis.* 1999;5(4):285-94. <https://doi.org/10.1097/00054725-199911000-00009>.
28. Schroder K, Hertzog PJ, Ravasi T, Hume DA. Interferon-gamma: An overview of signals, mechanisms and functions. *J Leukoc Biol.* 2004;75(2):163-89. <https://doi.org/10.1189/jlb.0603252>.
29. Balkwill F. Tumour necrosis factor and cancer. *Nat Rev Cancer.* 2009;9(5):361-71. <https://doi.org/10.1038/nrc2628>.
30. Hallermalm K, Seki K, Wei C, Castelli C, Rivoltini L, Kiessling R, et al. Tumor necrosis factor-alpha induces coordinated changes in major histocompatibility class i presentation pathway, resulting in increased stability of class i complexes at the cell surface. *Blood.* 2001;98(4):1108-15. <https://doi.org/10.1182/blood.v98.4.1108>.
31. Benveniste EN, Sparacio SM, Bethea JR. Tumor necrosis factor- α enhances interferon- γ -mediated class ii antigen expression on astrocytes. *J Neuroimmunol.* 1989;25(2):209-19. [https://doi.org/10.1016/0165-5728\(89\)90139-2](https://doi.org/10.1016/0165-5728(89)90139-2).
32. Golay J, Taylor RP. The role of complement in the mechanism of action of therapeutic anti-cancer mabs. *Antibodies (Basel).* 2020;9(4):58. <https://doi.org/10.3390/antib9040058>.
33. Rastogi I, Jeon D, Moseman JE, Muralidhar A, Potluri HK, McNeel DG. Role of b cells as antigen presenting cells. *Front Immunol.* 2022;13:954936. <https://doi.org/10.3389/fimmu.2022.954936>.
34. O'Sullivan D, Pearce EL. Targeting t cell metabolism for therapy. *Trends Immunol.* 2015;36(2):71-80. <https://doi.org/10.1016/j.it.2014.12.004>.
35. van der Windt GJ, Pearce EL. Metabolic switching and fuel choice during t-cell differentiation and memory development. *Immunol Rev.* 2012;249(1):27-42. <https://doi.org/10.1111/j.1600-065X.2012.01150.x>.
36. Palmer CS, Ostrowski M, Balderson B, Christian N, Crowe SM. Glucose metabolism regulates t cell activation, differentiation, and functions. *Front Immunol.* 2015;6:1. <https://doi.org/10.3389/fimmu.2015.00001>.
37. Wellen KE, Hatzivassiliou G, Sachdeva UM, Bui TV, Cross JR, Thompson CB. Atp-citrate lyase links cellular metabolism to histone acetylation. *Science.* 2009;324(5930):1076-80. <https://doi.org/10.1126/science.1164097>.
38. Ducker GS, Rabinowitz JD. One-carbon metabolism in health and disease. *Cell Metab.* 2017;25(1):27-42. <https://doi.org/10.1016/j.cmet.2016.08.009>.
39. Holeček M. Origin and roles of alanine and glutamine in gluconeogenesis in the liver, kidneys, and small intestine under physiological and pathological conditions. *Int J Mol Sci.* 2024;25(13):7037. <https://doi.org/10.3390/ijms25137037>.
40. Griffith OW, Miller RH. Mechanism of nitric oxide production. *Proc Natl Acad Sci U S A.* 1998 Mar 10;95(6):2994-2999.
41. Zhang L, Li S, Lin J. Glutamine metabolism in T cells. *Nat Rev Immunol.* 2016;16(10):702-711.
42. Buck MD, Sowell RT, Kaech SM, Pearce EL. Metabolic instruction of immunity. *Cell.* 2017;169(4):570-86. <https://doi.org/10.1016/j.cell.2017.04.004>.
43. Murray PJ, Wynn TA. Protective and pathogenic functions of macrophage subsets. *Nat Rev Immunol.* 2011;11(11):723-37. <https://doi.org/10.1038/nri3073>.
44. Biswas SK, Mantovani A. Macrophage plasticity and interaction with lymphocyte subsets: Cancer as a paradigm. *Nat Immunol.* 2010;11(10):889-96. <https://doi.org/10.1038/ni.1937>.
45. Munder M, Eichmann K, Morán JM, Centeno F, Soler G, Modolell M. Th1/th2-regulated expression of arginase isoforms in murine macrophages and dendritic cells. *J Immunol.* 1999;163(7):3771-7.
46. Colegio OR, Chu NQ, Szabo AL, Chu T, Rhebergen AM, Jairam V, et al. Functional polarization of tumour-associated macrophages by tumour-derived lactic acid. *Nature.* 2014;513(7519):559-63. <https://doi.org/10.1038/nature13490>.
47. Koo SJ, Garg NJ. Metabolic programming of macrophage functions and pathogens control. *Redox Biol.* 2019;24:101198. <https://doi.org/10.1016/j.redox.2019.101198>.
48. Banchereau J, Steinman R. Banchereau j, steinman rmdendritic cells the control of immunity. *Nature* 392:245-252. *Nature.* 1998;392:245-52. <https://doi.org/10.1038/32588>.
49. Möller SH, Wang L, Ho PC. Metabolic programming in dendritic cells tailors immune responses and homeostasis. *Cell Mol Immunol.* 2022;19(3):370-83. <https://doi.org/10.1038/s41423-021-00753-1>.
50. Gardner A, Ruffell B. Dendritic cells and cancer immunity. *Trends Immunol.* 2016;37(12):855-65. <https://doi.org/10.1016/j.it.2016.09.006>.
51. Morel PA, Turner MS. Dendritic cells and the maintenance of self-tolerance. *Immunol Res.* 2011;50(2-3):124-9. <https://doi.org/10.1007/s12026-011-8217-y>.
52. Wing K, Onishi Y, Prieto-Martin P, Yamaguchi T, Miyara M, Fehervari Z, et al. Ctla-4 control over foxp3+ regulatory t cell function. *Science.* 2008;322(5899):271-5. <https://doi.org/10.1126/science.1160062>.
53. Del Prete A, Salvi V, Soriani A, Laffranchi M, Sozio F, Bosisio D, et al. Dendritic cell subsets in cancer immunity and tumor

- antigen sensing. *Cell Mol Immunol*. 2023;20(5):432-47. <https://doi.org/10.1038/s41423-023-00990-6>.
54. Zong J, Keskinov AA, Shurin GV, Shurin MR. Tumor-derived factors modulating dendritic cell function. *Cancer Immunol Immunother*. 2016;65(7):821-33. <https://doi.org/10.1007/s00262-016-1820-y>.
 55. Seyfizadeh N, Muthuswamy R, Mitchell DA, Nierkens S, Seyfizadeh N. Migration of dendritic cells to the lymph nodes and its enhancement to drive anti-tumor responses. *Crit Rev Oncol Hematol*. 2016;107:100-10. <https://doi.org/10.1016/j.critrevonc.2016.09.002>.
 56. Krishnamoorthy M, Gerhardt L, Maleki Vareki S. Immunosuppressive effects of myeloid-derived suppressor cells in cancer and immunotherapy. *Cells*. 2021;10(5):1170. <https://doi.org/10.3390/cells10051170>.
 57. Maskalenko NA, Zhigarev D, Campbell KS. Harnessing natural killer cells for cancer immunotherapy: Dispatching the first responders. *Nat Rev Drug Discov*. 2022;21(8):559-77. <https://doi.org/10.1038/s41573-022-00413-7>.
 58. Wu J, Lanier LL. Natural killer cells and cancer. *Adv Cancer Res*. 2003;90:127-56. [https://doi.org/10.1016/s0065-230x\(03\)90004-2](https://doi.org/10.1016/s0065-230x(03)90004-2).
 59. Tie Y, Tang F, Wei YQ, Wei XW. Immunosuppressive cells in cancer: Mechanisms and potential therapeutic targets. *J Hematol Oncol*. 2022;15(1):61. <https://doi.org/10.1186/s13045-022-01282-8>.
 60. Portale F, Di Mitri D. Nk cells in cancer: Mechanisms of dysfunction and therapeutic potential. *Int J Mol Sci*. 2023;24(11):9521. <https://doi.org/10.3390/ijms24119521>.
 61. Wang D, Dou L, Sui L, Xue Y, Xu S. Natural killer cells in cancer immunotherapy. *MedComm* (2020). 2024;5(7):e626. <https://doi.org/10.1002/mco2.626>.
 62. Josefowicz SZ, Lu LF, Rudensky AY. Regulatory t cells: Mechanisms of differentiation and function. *Annu Rev Immunol*. 2012;30:531-64. <https://doi.org/10.1146/annurev.immunol.25.022106.141623>.
 63. Tomaszewicz M, Ronowska A, Zieliński M, Jankowska-Kulawy A, Trzonkowski P. T regulatory cells metabolism: The influence on functional properties and treatment potential. *Front Immunol*. 2023;14:1122063. <https://doi.org/10.3389/fimmu.2023.1122063>.
 64. Sakaguchi S, Yamaguchi T, Nomura T, Ono M. Regulatory t cells and immune tolerance. *Cell*. 2008;133(5):775-87. <https://doi.org/10.1016/j.cell.2008.05.009>.
 65. Vignali DA, Collison LW, Workman CJ. How regulatory t cells work. *Nat Rev Immunol*. 2008;8(7):523-32. <https://doi.org/10.1038/nri2343>.
 66. Grossman WJ, Verbsky JW, Barchet W, Colonna M, Atkinson JP, Ley TJ. Human t regulatory cells can use the perforin pathway to cause autologous target cell death. *Immunity*. 2004;21(4):589-601. <https://doi.org/10.1016/j.immuni.2004.09.002>.
 67. Deaglio S, Dwyer KM, Gao W, Friedman D, Usheva A, Erat A, et al. Adenosine generation catalyzed by cd39 and cd73 expressed on regulatory t cells mediates immune suppression. *J Exp Med*. 2007;204(6):1257-65. <https://doi.org/10.1084/jem.20062512>.
 68. Fallarino F, Grohmann U, Vacca C, Bianchi R, Orabona C, Spreca A, et al. T cell apoptosis by tryptophan catabolism. *Cell Death Differ*. 2002;9(10):1069-77. <https://doi.org/10.1038/sj.cdd.4401073>.
 69. Huang CT, Workman CJ, Flies D, Pan X, Marson AL, Zhou G, et al. Role of lag-3 in regulatory t cells. *Immunity*. 2004;21(4):503-13. <https://doi.org/10.1016/j.immuni.2004.08.010>.
 70. Renner K, Singer K, Koehl GE, Geissler EK, Peter K, Siska PJ, et al. Metabolic hallmarks of tumor and immune cells in the tumor microenvironment. *Front Immunol*. 2017;8:248. <https://doi.org/10.3389/fimmu.2017.00248>.
 71. Xiao L, Wang Q, Peng H. Tumor-associated macrophages: New insights on their metabolic regulation and their influence in cancer immunotherapy. *Front Immunol*. 2023;14:1157291. <https://doi.org/10.3389/fimmu.2023.1157291>.
 72. Kumar V, Gabrilovich DI. Hypoxia-inducible factors in regulation of immune responses in tumour microenvironment. *Immunology*. 2014;143(4):512-9. <https://doi.org/10.1111/imm.12380>.
 73. Noy R, Pollard JW. Tumor-associated macrophages: From mechanisms to therapy. *Immunity*. 2014;41(1):49-61. <https://doi.org/10.1016/j.immuni.2014.06.010>.
 74. Jaynes JM, Sable R, Ronzetti M, Bautista W, Knotts Z, Abisoye-Ogunniyan A, et al. Mannose receptor (cd206) activation in tumor-associated macrophages enhances adaptive and innate antitumor immune responses. *Sci Transl Med*. 2020;12(530). <https://doi.org/10.1126/scitranslmed.aax6337>.
 75. Wang SC, Hong JH, Hsueh C, Chiang CS. Tumor-secreted sdf-1 promotes glioma invasiveness and tropism toward hypoxia in a murine astrocytoma model. *Lab Invest*. 2012;92(1):151-62. <https://doi.org/10.1038/labinvest.2011.128>.
 76. Sawa-Wejksza K, Kandefer-Szerszeń M. Tumor-associated macrophages as target for antitumor therapy. *Arch Immunol Ther Exp (Warsz)*. 2018;66(2):97-111. <https://doi.org/10.1007/s00005-017-0480-8>.
 77. He Z, Zhang S. Tumor-associated macrophages and their functional transformation in the hypoxic tumor microenvironment. *Front Immunol*. 2021;12:741305. <https://doi.org/10.3389/fimmu.2021.741305>.
 78. Wang Y, Wang D, Yang L, Zhang Y. Metabolic reprogramming in the immunosuppression of tumor-associated macrophages. *Chin Med J (Engl)*. 2022;135(20):2405-16. <https://doi.org/10.1097/cm9.0000000000002426>.
 79. Dirx AE, Oude Egbrink MG, Wagstaff J, Griffioen AW. Monocyte/macrophage infiltration in tumors: Modulators of angiogenesis. *J Leukoc Biol*. 2006;80(6):1183-96. <https://doi.org/10.1189/jlb.0905495>.
 80. Pu Y, Ji Q. Tumor-associated macrophages regulate pd-1/pd-l1 immunosuppression. *Front Immunol*. 2022;13:874589. <https://doi.org/10.3389/fimmu.2022.874589>.
 81. Bronte V, Brandau S, Chen SH, Colombo MP, Frey AB, Greten TF, et al. Recommendations for myeloid-derived suppressor cell nomenclature and characterization standards. *Nat Commun*. 2016;7:12150. <https://doi.org/10.1038/ncomms12150>.
 82. Gabrilovich DI, Nagaraj S. Myeloid-derived suppressor cells as regulators of the immune system. *Nat Rev Immunol*. 2009;9(3):162-74. <https://doi.org/10.1038/nri2506>.
 83. Condamine T, Ramachandran I, Youn JI, Gabrilovich DI. Regulation of tumor metastasis by myeloid-derived suppressor cells. *Annu Rev Med*. 2015;66:97-110. <https://doi.org/10.1146/annurev-med-051013-052304>.
 84. Li W, Zhang X, Chen Y, Xie Y, Liu J, Feng Q, et al. G-csf is a key modulator of mdsc and could be a potential therapeutic target in colitis-associated colorectal cancers. *Protein Cell*. 2016;7(2):130-40. <https://doi.org/10.1007/s13238-015-0237-2>.
 85. Cheng P, Corzo CA, Luetsteke N, Yu B, Nagaraj S, Bui MM, et al. Inhibition of dendritic cell differentiation and accumulation of myeloid-derived suppressor cells in cancer is regulated by s100a9 protein. *J Exp Med*. 2008;205(10):2235-49. <https://doi.org/10.1084/jem.20080132>.
 86. Munn DH, Mellor AL. Indoleamine 2,3-dioxygenase and tumor-induced tolerance. *J Clin Invest*. 2007;117(5):1147-

54. <https://doi.org/10.1172/jci31178>.
87. Rodriguez PC, Quiceno DG, Zabaleta J, Ortiz B, Zea AH, Piazuelo MB, et al. Arginase i production in the tumor microenvironment by mature myeloid cells inhibits t-cell receptor expression and antigen-specific t-cell responses. *Cancer Res.* 2004;64(16):5839-49. <https://doi.org/10.1158/0008-5472.Can-04-0465>.
88. Yaseen MM, Abuharfeil NM, Darmani H, Daoud A. Mechanisms of immune suppression by myeloid-derived suppressor cells: The role of interleukin-10 as a key immunoregulatory cytokine. *Open Biol.* 2020;10(9):200111. <https://doi.org/10.1098/rsob.200111>.
89. Husain Z, Seth P, Sukhatme VP. Tumor-derived lactate and myeloid-derived suppressor cells: Linking metabolism to cancer immunology. *Oncoimmunology.* 2013;2(11):e26383. <https://doi.org/10.4161/onci.26383>.
90. Kumar V, Patel S, Tcyganov E, Gabrilovich DI. The nature of myeloid-derived suppressor cells in the tumor microenvironment. *Trends Immunol.* 2016;37(3):208-20. <https://doi.org/10.1016/j.it.2016.01.004>.
91. Joshi S, Sharabi A. Targeting myeloid-derived suppressor cells to enhance natural killer cell-based immunotherapy. *Pharmacol Ther.* 2022;235:108114. <https://doi.org/10.1016/j.pharmthera.2022.108114>.
92. Kim JH, Kim BS, Lee SK. Regulatory t cells in tumor microenvironment and approach for anticancer immunotherapy. *Immune Netw.* 2020;20(1):e4. <https://doi.org/10.4110/in.2020.20.e4>.
93. Lee GR. Phenotypic and functional properties of tumor-infiltrating regulatory t cells. *Mediators Inflamm.* 2017;2017:5458178. <https://doi.org/10.1155/2017/5458178>.
94. Yu T, Dong T, Eyvani H, Fang Y, Wang X, Zhang X, et al. Metabolic interventions: A new insight into the cancer immunotherapy. *Arch Biochem Biophys.* 2021;697:108659. <https://doi.org/10.1016/j.abb.2020.108659>.
95. Rao D, Verburg F, Renner K, Peeper DS, Lacroix R, Blank CU. Metabolic profiles of regulatory t cells in the tumour microenvironment. *Cancer Immunol Immunother.* 2021;70(9):2417-27. <https://doi.org/10.1007/s00262-021-02881-z>.
96. Kurniawan H, Soriano-Baguet L, Brenner D. Regulatory t cell metabolism at the intersection between autoimmune diseases and cancer. *Eur J Immunol.* 2020;50(11):1626-42. <https://doi.org/10.1002/eji.201948470>.
97. Shan Y, Xie T, Sun Y, Lu Z, Topatana W, Juengpanich S, et al. Lipid metabolism in tumor-infiltrating regulatory t cells: Perspective to precision immunotherapy. *Biomark Res.* 2024;12(1):41. <https://doi.org/10.1186/s40364-024-00588-8>.
98. Bulygin AS, Khantakova JN, Shkaruba NS, Shiku H, Sennikov SS. The role of metabolism on regulatory t cell development and its impact in tumor and transplantation immunity. *Front Immunol.* 2022;13:1016670. <https://doi.org/10.3389/fimmu.2022.1016670>.
99. Park K, Veena MS, Shin DS. Key players of the immunosuppressive tumor microenvironment and emerging therapeutic strategies. *Front Cell Dev Biol.* 2022;10:830208. <https://doi.org/10.3389/fcell.2022.830208>.
100. Gu J, Zhou J, Chen Q, Xu X, Gao J, Li X, et al. Tumor metabolite lactate promotes tumorigenesis by modulating moesin lactylation and enhancing tgf- β signaling in regulatory t cells. *Cell Rep.* 2022;39(12):110986. <https://doi.org/10.1016/j.celrep.2022.110986>.
101. Kumagai S, Koyama S, Itahashi K, Tanegashima T, Lin YT, Togashi Y, et al. Lactic acid promotes pd-1 expression in regulatory t cells in highly glycolytic tumor microenvironments. *Cancer Cell.* 2022;40(2):201-18.e9. <https://doi.org/10.1016/j.ccell.2022.01.001>.
102. Ding R, Yu X, Hu Z, Dong Y, Huang H, Zhang Y, et al. Lactate modulates rna splicing to promote ctla-4 expression in tumor-infiltrating regulatory t cells. *Immunity.* 2024;57(3):528-40.e6. <https://doi.org/10.1016/j.immuni.2024.01.019>.
103. Jiang X, Wu X, Xiao Y, Wang P, Zheng J, Wu X, et al. The ectonucleotidases cd39 and cd73 on t cells: The new pillar of hematological malignancy. *Front Immunol.* 2023;14:1110325. <https://doi.org/10.3389/fimmu.2023.1110325>.
104. Huang L, Guo Y, Liu S, Wang H, Zhu J, Ou L, et al. Targeting regulatory t cells for immunotherapy in melanoma. *Mol Biomed.* 2021;2(1):11. <https://doi.org/10.1186/s43556-021-00038-z>.
105. Rodríguez-Guilarte L, Ramírez MA, Andrade CA, Kalergis AM. Lag-3 contribution to t cell downmodulation during acute respiratory viral infections. *Viruses.* 2023;15(1):147. <https://doi.org/10.3390/v15010147>.
106. Tomasek JJ, Gabbiani G, Hinz B, Chaponnier C, Brown RA. Myofibroblasts and mechano-regulation of connective tissue remodelling. *Nat Rev Mol Cell Biol.* 2002;3(5):349-63. <https://doi.org/10.1038/nrm809>.
107. Hinz B. Formation and function of the myofibroblast during tissue repair. *J Invest Dermatol.* 2007;127(3):526-37. <https://doi.org/10.1038/sj.jid.5700613>.
108. Kalluri R, Zeisberg M. Fibroblasts in cancer. *Nat Rev Cancer.* 2006;6(5):392-401. <https://doi.org/10.1038/nrc1877>.
109. Avagliano A, Granato G, Ruocco MR, Romano V, Belviso I, Carfora A, et al. Metabolic reprogramming of cancer associated fibroblasts: The slavery of stromal fibroblasts. *Biomed Res Int.* 2018;2018:6075403. <https://doi.org/10.1155/2018/6075403>.
110. Joshi RS, Kanugula SS, Sudhir S, Pereira MP, Jain S, Aghi MK. The role of cancer-associated fibroblasts in tumor progression. *Cancers (Basel).* 2021;13(6):1399. <https://doi.org/10.3390/cancers13061399>.
111. Ermakov MS, Nushtaeva AA, Richter VA, Koval OA. Cancer-associated fibroblasts and their role in tumor progression. *Vavilovskii Zhurnal Genet Selektcii.* 2022;26(1):14-21. <https://doi.org/10.18699/vjgb-22-03>.
112. Yang Y, Li C, Liu T, Dai X, Bazhin AV. Myeloid-derived suppressor cells in tumors: From mechanisms to antigen specificity and microenvironmental regulation. *Front Immunol.* 2020;11:1371. <https://doi.org/10.3389/fimmu.2020.01371>.
113. Koppensteiner L, Mathieson L, O'Connor RA, Akram AR. Cancer associated fibroblasts - an impediment to effective anti-cancer t cell immunity. *Front Immunol.* 2022;13:887380. <https://doi.org/10.3389/fimmu.2022.887380>.
114. Saw PE, Chen J, Song E. Targeting cdfs to overcome anticancer therapeutic resistance. *Trends Cancer.* 2022;8(7):527-55. <https://doi.org/10.1016/j.trecan.2022.03.001>.
115. Phan LM, Yeung SC, Lee MH. Cancer metabolic reprogramming: Importance, main features, and potentials for precise targeted anti-cancer therapies. *Cancer Biol Med.* 2014;11(1):1-19. <https://doi.org/10.7497/j.issn.2095-3941.2014.01.001>.
116. Ginefra P, Carrasco Hope H, Spagna M, Zecchillo A, Vannini N. Ionic regulation of t-cell function and anti-tumour immunity. *Int J Mol Sci.* 2021;22(24). <https://doi.org/10.3390/ijms222413668>.
117. Lieu EL, Nguyen T, Rhyne S, Kim J. Amino acids in cancer. *Exp Mol Med.* 2020;52(1):15-30. <https://doi.org/10.1038/s12276-020-0375-3>.
118. Sung JY, Cheong JH. New immunometabolic strategy based on cell type-specific metabolic reprogramming in the tumor

- immune microenvironment. *Cells*. 2022;11(5). <https://doi.org/10.3390/cells11050768>.
119. van Baren N, Van den Eynde BJ. Tryptophan-degrading enzymes in tumoral immune resistance. *Front Immunol*. 2015;6:34. <https://doi.org/10.3389/fimmu.2015.00034>.
 120. Hashemzadeh N, Adibkia K, Barar J. Indoleamine 2, 3-dioxygenase inhibitors in immunochemotherapy of breast cancer: Challenges and opportunities. *Bioimpacts*. 2019;9(1):1-3. <https://doi.org/10.15171/bi.2019.01>.
 121. Yue EW, Sparks R, Polam P, Modi D, Douty B, Wayland B, et al. Incb24360 (epacadostat), a highly potent and selective indoleamine-2,3-dioxygenase 1 (ido1) inhibitor for immunoncology. *ACS Med Chem Lett*. 2017;8(5):486-91. <https://doi.org/10.1021/acsmchemlett.6b00391>.
 122. Zhou X, Zhu X, Zeng H. Fatty acid metabolism in adaptive immunity. *Febs j*. 2023;290(3):584-99. <https://doi.org/10.1111/febs.16296>.
 123. Pacella I, Procaccini C, Focacetti C, Miacci S, Timperi E, Faicchia D, et al. Fatty acid metabolism complements glycolysis in the selective regulatory t cell expansion during tumor growth. *Proc Natl Acad Sci U S A*. 2018;115(28):E6546-e55. <https://doi.org/10.1073/pnas.1720113115>.
 124. Wegiel B, Vuerich M, Daneshmandi S, Seth P. Metabolic switch in the tumor microenvironment determines immune responses to anti-cancer therapy. *Front Oncol*. 2018;8:284. <https://doi.org/10.3389/fonc.2018.00284>.
 125. Abou Khouzam R, Brodaczevska K, Filipiak A, Zeinelabdin NA, Buart S, Szczylik C, et al. Tumor hypoxia regulates immune escape/invasion: Influence on angiogenesis and potential impact of hypoxic biomarkers on cancer therapies. *Front Immunol*. 2020;11:613114. <https://doi.org/10.3389/fimmu.2020.613114>.
 126. Chouaib S, Messai Y, Couve S, Escudier B, Hasmmim M, Noman MZ. Hypoxia promotes tumor growth in linking angiogenesis to immune escape. *Front Immunol*. 2012;3:21. <https://doi.org/10.3389/fimmu.2012.00021>.
 127. Singh D, Arora R, Kaur P, Singh B, Mannan R, Arora S. Overexpression of hypoxia-inducible factor and metabolic pathways: Possible targets of cancer. *Cell Biosci*. 2017;7:62. <https://doi.org/10.1186/s13578-017-0190-2>.
 128. Martin JD, Seano G, Jain RK. Normalizing function of tumor vessels: Progress, opportunities, and challenges. *Annu Rev Physiol*. 2019;81:505-34. <https://doi.org/10.1146/annurev-physiol-020518-114700>.
 129. Yu X, Gao R, Li Y, Zeng C. Regulation of pd-1 in t cells for cancer immunotherapy. *Eur J Pharmacol*. 2020;881:173240. <https://doi.org/10.1016/j.ejphar.2020.173240>.
 130. Bailey CM, Liu Y, Liu M, Du X, Devenport M, Zheng P, et al. Targeting hif-1 α abrogates pd-1-mediated immune evasion in tumor microenvironment but promotes tolerance in normal tissues. *J Clin Invest*. 2022;132(9). <https://doi.org/10.1172/jci150846>.
 131. Li K, Shi H, Zhang B, Ou X, Ma Q, Chen Y, et al. Myeloid-derived suppressor cells as immunosuppressive regulators and therapeutic targets in cancer. *Signal Transduct Target Ther*. 2021;6(1):362. <https://doi.org/10.1038/s41392-021-00670-9>.
 132. Sasidharan Nair V, Saleh R, Toor SM, Cyprian FS, Elkord E. Metabolic reprogramming of t regulatory cells in the hypoxic tumor microenvironment. *Cancer Immunol Immunother*. 2021;70(8):2103-21. <https://doi.org/10.1007/s00262-020-02842-y>.
 133. Liu Y, Li Z, Zhao X, Xiao J, Jiacheng B, Li X-Y, et al. Review immune response of targeting cd39 in cancer. *Biomark Res*. 2023;11. <https://doi.org/10.1186/s40364-023-00500-w>.
 134. Forte G, Sorrentino R, Montinaro A, Luciano A, Adcock IM, Maiolino P, et al. Inhibition of cd73 improves b cell-mediated anti-tumor immunity in a mouse model of melanoma. *J Immunol*. 2012;189(5):2226-33. <https://doi.org/10.4049/jimmunol.1200744>.
 135. Ryzhov S, Novitskiy SV, Goldstein AE, Biktasova A, Blackburn MR, Biaggioni I, et al. Adenosinergic regulation of the expansion and immunosuppressive activity of cd11b+gr1+ cells. *J Immunol*. 2011;187(11):6120-9. <https://doi.org/10.4049/jimmunol.1101225>.
 136. Hatfield SM, Sitkovsky M. A2a adenosine receptor antagonists to weaken the hypoxia-hif-1 α driven immunosuppression and improve immunotherapies of cancer. *Curr Opin Pharmacol*. 2016;29:90-6. <https://doi.org/10.1016/j.coph.2016.06.009>.
 137. Romero-Garcia S, Moreno-Altamirano MM, Prado-Garcia H, Sánchez-García FJ. Lactate contribution to the tumor microenvironment: Mechanisms, effects on immune cells and therapeutic relevance. *Front Immunol*. 2016;7:52. <https://doi.org/10.3389/fimmu.2016.00052>.
 138. Wang ZH, Peng WB, Zhang P, Yang XP, Zhou Q. Lactate in the tumour microenvironment: From immune modulation to therapy. *EBioMedicine*. 2021;73:103627. <https://doi.org/10.1016/j.ebiom.2021.103627>.
 139. Mishra D, Banerjee D. Lactate dehydrogenases as metabolic links between tumor and stroma in the tumor microenvironment. *Cancers (Basel)*. 2019;11(6). <https://doi.org/10.3390/cancers11060750>.
 140. Gao Y, Zhou H, Liu G, Wu J, Yuan Y, Shang A. Tumor microenvironment: Lactic acid promotes tumor development. *J Immunol Res*. 2022;2022:3119375. <https://doi.org/10.1155/2022/3119375>.
 141. Husain Z, Huang Y, Seth P, Sukhatme VP. Tumor-derived lactate modifies antitumor immune response: Effect on myeloid-derived suppressor cells and nk cells. *J Immunol*. 2013;191(3):1486-95. <https://doi.org/10.4049/jimmunol.1202702>.
 142. Fischer K, Hoffmann P, Voelkl S, Meidenbauer N, Ammer J, Edinger M, et al. Inhibitory effect of tumor cell-derived lactic acid on human t cells. *Blood*. 2007;109(9):3812-9. <https://doi.org/10.1182/blood-2006-07-035972>.
 143. Koudhi S, Ben Ayed F, Benammar Elgaaied A. Targeting tumor metabolism: A new challenge to improve immunotherapy. *Front Immunol*. 2018;9:353. <https://doi.org/10.3389/fimmu.2018.00353>.
 144. Ganapathy-Kanniappan S, Vali M, Kunjithapatham R, Buijs M, Syed LH, Rao PP, et al. 3-bromopyruvate: A new targeted antiglycolytic agent and a promise for cancer therapy. *Curr Pharm Biotechnol*. 2010;11(5):510-7. <https://doi.org/10.2174/138920110791591427>.
 145. León-Letelier RA, Dou R, Vykoukal J, Sater AHA, Ostrin E, Hanash S, et al. The kynurenine pathway presents multi-faceted metabolic vulnerabilities in cancer. *Front Oncol*. 2023;13:1256769. <https://doi.org/10.3389/fonc.2023.1256769>.
 146. Fujiwara Y, Kato S, Nesline MK, Conroy JM, DePietro P, Pabla S, et al. Indoleamine 2,3-dioxygenase (ido) inhibitors and cancer immunotherapy. *Cancer Treat Rev*. 2022;110:102461. <https://doi.org/10.1016/j.ctrv.2022.102461>.
 147. Zahavi D, Hodge JW. Targeting immunosuppressive adenosine signaling: A review of potential immunotherapy combination strategies. *Int J Mol Sci*. 2023;24(10). <https://doi.org/10.3390/ijms24108871>.
 148. Richon VM, Emiliani S, Verdin E, Webb Y, Breslow R, Rifkind RA, et al. A class of hybrid polar inducers of transformed cell differentiation inhibits histone deacetylases.

- Proc Natl Acad Sci U S A. 1998;95(6):3003-7. <https://doi.org/10.1073/pnas.95.6.3003>.
149. Sikalidis AK. Amino acids and immune response: A role for cysteine, glutamine, phenylalanine, tryptophan and arginine in t-cell function and cancer? *Pathol Oncol Res*. 2015;21(1):9-17. <https://doi.org/10.1007/s12253-014-9860-0>.
150. Marti ILAA, Reith W. Arginine-dependent immune responses. *Cell Mol Life Sci*. 2021;78(13):5303-24. <https://doi.org/10.1007/s00018-021-03828-4>.
151. Muranaka H, Akinsola R, Billet S, Pandol SJ, Hendifar AE, Bhowmick NA, et al. Glutamine supplementation as an anticancer strategy: A potential therapeutic alternative to the convention. *Cancers (Basel)*. 2024;16(5). <https://doi.org/10.3390/cancers16051057>.
152. Habtetsion T, Zhou G. Exploiting metabolic inhibition to eradicate residual tumors after chemo-immunotherapy. *J Immunother Cancer*. 2014;2:P208-P. <https://doi.org/10.1186/2051-1426-2-S3-P208>.
153. Akinleye A, Rasool Z. Immune checkpoint inhibitors of pd-1 as cancer therapeutics. *J Hematol Oncol*. 2019;12(1):92. <https://doi.org/10.1186/s13045-019-0779-5>.
154. Fessas P, Lee H, Ikemizu S, Janowitz T. A molecular and preclinical comparison of the pd-1-targeted t-cell checkpoint inhibitors nivolumab and pembrolizumab. *Semin Oncol*. 2017;44(2):136-40. <https://doi.org/10.1053/j.seminoncol.2017.06.002>.
155. Rotte A. Combination of ctla-4 and pd-1 blockers for treatment of cancer. *J Exp Clin Cancer Res*. 2019;38(1):255. <https://doi.org/10.1186/s13046-019-1259-z>.
156. Savoia P, Astrua C, Fava P. Ipilimumab (anti-ctla-4 mab) in the treatment of metastatic melanoma: Effectiveness and toxicity management. *Hum Vaccin Immunother*. 2016;12(5):1092-101. <https://doi.org/10.1080/21645515.2015.1129478>.
157. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med*. 2010;363(8):711-23. <https://doi.org/10.1056/NEJMoa1003466>.
158. Zang YW, Gu XD, Xiang JB, Chen ZY. Clinical application of adoptive t cell therapy in solid tumors. *Med Sci Monit*. 2014;20:953-9. <https://doi.org/10.12659/msm.890496>.
159. Tomuleasa C, Fuji S, Berce C, Onaciu A, Chira S, Petrushev B, et al. Chimeric antigen receptor t-cells for the treatment of b-cell acute lymphoblastic leukemia. *Front Immunol*. 2018;9:239. <https://doi.org/10.3389/fimmu.2018.00239>.
160. Feldman SA, Assadipour Y, Kriley I, Goff SL, Rosenberg SA. Adoptive cell therapy--tumor-infiltrating lymphocytes, t-cell receptors, and chimeric antigen receptors. *Semin Oncol*. 2015;42(4):626-39. <https://doi.org/10.1053/j.seminoncol.2015.05.005>.
161. Molon B, Cali B, Viola A. T cells and cancer: How metabolism shapes immunity. *Front Immunol*. 2016;7:20. <https://doi.org/10.3389/fimmu.2016.00020>.
162. Rosenberg SA, Yang JC, Sherry RM, Kammula US, Hughes MS, Phan GQ, et al. Durable complete responses in heavily pretreated patients with metastatic melanoma using t-cell transfer immunotherapy. *Clin Cancer Res*. 2011;17(13):4550-7. <https://doi.org/10.1158/1078-0432.Ccr-11-0116>.
163. Morgan MA, Schambach A. Engineering car-t cells for improved function against solid tumors. *Front Immunol*. 2018;9:2493. <https://doi.org/10.3389/fimmu.2018.02493>.
164. Spolski R, Li P, Leonard WJ. Biology and regulation of il-2: From molecular mechanisms to human therapy. *Nat Rev Immunol*. 2018;18(10):648-59. <https://doi.org/10.1038/s41577-018-0046-y>.
165. Klapper JA, Downey SG, Smith FO, Yang JC, Hughes MS, Kammula US, et al. High-dose interleukin-2 for the treatment of metastatic renal cell carcinoma : A retrospective analysis of response and survival in patients treated in the surgery branch at the national cancer institute between 1986 and 2006. *Cancer*. 2008;113(2):293-301. <https://doi.org/10.1002/cncr.23552>.
166. Fenton SE, Saleiro D, Platanias LC. Type i and ii interferons in the anti-tumor immune response. *Cancers (Basel)*. 2021;13(5):1037. <https://doi.org/10.3390/cancers13051037>.
167. Shi W, Yao X, Fu Y, Wang Y. Interferon- α and its effects on cancer cell apoptosis. *Oncol Lett*. 2022;24(1):235. <https://doi.org/10.3892/ol.2022.13355>.
168. Handy CE, Antonarakis ES. Sipuleucel-t for the treatment of prostate cancer: Novel insights and future directions. *Future Oncol*. 2018;14(10):907-17. <https://doi.org/10.2217/fon-2017-0531>.
169. Banchereau J, Palucka AK. Dendritic cells as therapeutic vaccines against cancer. *Nat Rev Immunol*. 2005;5(4):296-306. <https://doi.org/10.1038/nri1592>.
170. Carmeliet P. Vegf as a key mediator of angiogenesis in cancer. *Oncology*. 2005;69 Suppl 3:4-10. <https://doi.org/10.1159/000088478>.
171. Ferrara N. Vascular endothelial growth factor. *Arterioscler Thromb Vasc Biol*. 2009;29(6):789-91. <https://doi.org/10.1161/atvbaha.108.179663>.
172. Jain RK. Normalizing tumor vasculature with anti-angiogenic therapy: A new paradigm for combination therapy. *Nat Med*. 2001;7(9):987-9. <https://doi.org/10.1038/nm0901-987>.
173. Jiang Z, Hsu JL, Li Y, Hortobagyi GN, Hung MC. Cancer cell metabolism bolsters immunotherapy resistance by promoting an immunosuppressive tumor microenvironment. *Front Oncol*. 2020;10:1197. <https://doi.org/10.3389/fonc.2020.01197>.
174. Steggerda SM, Bennett MK, Chen J, Emberley E, Huang T, Janes JR, et al. Inhibition of arginase by cb-1158 blocks myeloid cell-mediated immune suppression in the tumor microenvironment. *J Immunother Cancer*. 2017;5(1):101. <https://doi.org/10.1186/s40425-017-0308-4>.
175. Daneshmandi S, Wegiel B, Seth P. Blockade of lactate dehydrogenase-a (ldh-a) improves efficacy of anti-programmed cell death-1 (pd-1) therapy in melanoma. *Cancers (Basel)*. 2019;11(4):450. <https://doi.org/10.3390/cancers11040450>.
176. Sharma P, Hu-Lieskovan S, Wargo JA, Ribas A. Primary, adaptive, and acquired resistance to cancer immunotherapy. *Cell*. 2017;168(4):707-23. <https://doi.org/10.1016/j.cell.2017.01.017>.



This work is licensed under a Creative Commons Attribution-Non Commercial 4.0 International License.