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REVIEW ARTICLE

The interaction between end-metabolites and immune escape

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Abstract

Emerging data from metabolites-relating trails in cancers demonstrate that a common mechanism of resistance to many novel classes of immune therapeutics is the emergence of immune escape due to the reprogramming of cellular metabolism. Among them, current work about end-metabolites mostly focuses on the intersection between lactate acid, adenosine, reactive oxygen species (ROS), and tumour immune escape. In this article, we aim to review the evidence to date for the dynamic interplay between the three end-metabolites and tumour immune escape for potential approaches to overcome obstacles in the efficacy and durability of immune cancer therapies. We have organized known end-metabolites-associated immune escape mechanisms into three hallmarks: (1) decreased immunogenicity of cancer cells which constitutes defective antigen presentation and the attenuated expression of costimulatory molecules on tumour cells, (2) immunosuppressive microenvironment with aberrant angiogenesis inhibits the differentiation, maturation, and immune deviation of immune cells while drives the activation of immunosuppressive cells by immune-suppressive mediators (cytokines and other factors), (3) immune tolerance retained by inhibitory molecules and depletion of immune cells.

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Key words: lactate acid; adenosine; reactive oxygen species; tumour; immune escape

Introduction

Cancer immunotherapies, such as immune adoptive T cell transfer and checkpoint blockade, have drastically improved the clinical outcomes for multiple treatment-refractory and metastatic cancers. Although these immunotherapies have demonstrated durable responses, patient response rates remain suboptimal owing to undefined suppression mechanisms. Simultaneously, the field of cancer metabolic alterations has become a topic of interest in the past decade. Aided by new molecular, biological, and biochemical tools, studies on cancer cell metabolism have advanced our understanding of the mechanisms and functional influences of tumor-associated metabolic alterations at distinct stages of tumorigenesis. Therefore, there is increasing interest in elucidating the potential impact of metabolic alterations on the immunity of tumors, because unveiling the interplay may facilitate more potent antitumor therapies.

Distinct hallmarks of tumorigenesis-associated metabolic reprogramming exist. Tumor masses often grow under hypoxic conditions, lacking glucose and other nutrients; thus, the tumor microenvironment (TME) is usually characterized by lower pH values [1]. In addition to glucose, energy can also be generated through the glutaminolysis pathway. Thus, high amounts of lactic acid are produced by both pathways and subsequently discharged into the TME. An acidic TME results from the excessive and continuous generation of lactic acid [2]. One of the most abundant extracellular metabolites is adenosine owing to the significant generation of adenosine triphosphate (ATP). Adenosine in the TME is a result of active transport through the plasma membrane or extracellular ATP dephosphorylation through the concerted function of two ectonucleotidases, CD39 and CD73 [3]. The third extensively studied end-metabolite is the reactive oxygen species (ROS). ROS can be derived as by-products from mitochondria during ATP generation in the electron transport chain (ETC), or they can represent products in enzymatic reactions mainly under the mediation of NADPH oxidase (NOX) and dual oxidase (DUOX) families (e.g., GPX) [4]. Cancer cells

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reprogram their metabolism to adapt and survive in harsh environments and, in some pathways, even utilize such adverse conditions to their benefit [5, 6]. Therefore, these metabolites may not simply be waste products of cancer metabolism, as they have widespread effects on cancer biology, such as stimulating angiogenesis, local invasion, and metastasis. In addition to reprogramming energy metabolism, evading immune destruction has also been recently described as a hallmark of tumorigenesis [6, 7]. Tumor cells evade immune surveillance and elimination using two main strategies: eluding the anticancer immunity of the immune system and promoting an immunosuppressive TME [8, 9]. The TME comprises various types of immune cells, including regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and tumor-associated macrophages (TAMs), which concurrently attenuate the immune response to cancers, allowing for greater local invasion, metastasis, and occurrence of drug resistance [10, 11]. Immune cells such as macrophages and neutrophils have two subtypes: M1 and M2, and N1 and N2, respectively. M1 and N1 cells are typically activated cells that have pro-inflammatory features with antitumor activity, whereas M2 and N2 cells are immunosuppressive phenotypes that are alternatively activated to promote cancer progression.

This review focuses on the current advances in the identification of the complex and dynamic roles of lactate, adenosine, and ROS in tumor immunity. We discuss the mechanistic processes by which these three metabolites help cancer cells evade immune surveillance, break immune equilibrium, and finally escape immunity, thereby assisting tumor progression.

Lactate

The centrality of the Warburg effect in tumor metabolism has been well acknowledged [12, 13]. In accordance with the Warburg effect, the accumulation of the metabolite lactic acid and the subsequent acidic TME are the results of enhanced glycolysis. The metabolic switch of accelerated glycolysis in cancer cells is subtly mediated by increased expression levels of oncogenes, primarily hypoxia-inducible factor (HIF)-1α and c-Myc [14, 15]. In addition, to generate from aerobic glycolysis, tumor-derived lactic acid can also be produced from the catabolism of glutamine [16]. Thus, both the major pathway of aerobic glycolysis and the minor pathway of glutaminolysis are responsible for lactic acid production in cancer cells. In an acidic TME, an inverted H^+ gradient ($pH_{intracellular} > pH_{extracellular}$) is maintained by the corporate action of various transporters, such as monocarboxylic transporters (MCTs), Na^+/H^+ exchangers, H^+/K^+-ATPases, Na^+/HCO_3^- cotransporters, and carbonic anhydrases (CA IX and CA XII). This concentration inversion has been suggested to provide at least two benefits for cancer cells: (1) intracellular alkalization facilitates increased glycolysis, particularly in hypoxia, which promotes cancer cell proliferation [17]; (2) extracellular acidification hampers the initiation of an appropriate immune response [18]. Further, MCT1 and MCT4, which transport H^+-coupled molecules that contain a single carboxylate group such as lactate, pyruvate, β-hydroxybutyrate, and acetoacetate, are ubiquitously expressed in various cells, but are highly upregulated in cancer cells, where they connote a poor prognosis [19, 20]. Increased lactic acid accumulation and subsequent acidification of the TME promote multiple critical oncogenic processes, including invasion, metastasis, angiogenesis, and drug resistance. In this review, we specifically elaborate on how lactate enables cancer cells to survive immunosurveillance and elimination.

Immunogenicity

Tumor immunogenicity is the ability to induce different levels of adaptive immune responses and is dictated by two major criteria: antigen presentation and immune cell recognition. Weak immunogenicity elicits a suboptimal immune response that spares the opportunity and time for tumor cells to develop immune escape mechanisms [21]. Antigen presentation is the process by which antigen-presenting cells (APCs), such as dendritic cells (DCs), internalize tumor antigens and then present antigens to helper T (Th) cells to initiate an adaptive immune response. The recognition process is fueled by T cell receptor (TCR) and major histocompatibility complex (MHC) binding, costimulatory molecules, and some cytokines.

Presentation

Acidic and hypertonic micromilieu limit the capacity of DCs to present tumor antigens, thereby potentially contributing to cancer immune escape and partially accounting for poor clinical response to DC vaccines [22]. Moreover, the TME contains abundant immunosuppressive factors that impair the immunostimulatory capacity of DCs [23]. Exposure to high levels of lactate (e.g., 40 mM) was confirmed to hamper the differentiation and maturation of DCs [14]. As a result, the presentation of DCs is affected. In addition to the aberrant development of DCs, studies have also documented that peptide-MHC I complexes are unstable at acidic pH compared to neutral pH [15], which results in faster Ag release. The third mechanism may be that lactic acid induces a significant reduction in interleukin (IL)-12 in tumor-associated DCs, which triggers a blockage of an important stimulatory signal in the cross-priming cascade of DCs [14, 23].

Recognition

In a recent study, lactic acid suppressed the proliferation of human cytotoxic T lymphocytes (CTLs) up to 95% and led to a 50% decrease in cytotoxic cytokine production. Therefore, lactic acid promotes the development of immune evasion by establishing an anergic state of tumor-specific $CD8^+$ T lymphocytes. This is characterized by decreased cytolytic activity and cytokine secretion owing to reduced expression levels of TCRs and IL-2Ra (CD25), and diminished activation of extracellular signal-regulated kinase (ERK) and STAT5 after TCR activation both in human and mouse models [24]. Another reason for the decreased CTL function is ascribed to lactate dehydrogenase A (LDHA), which is highly expressed in cancer cells by the mediation of c-Myc and HIF-1α [23, 25]. LDHA was experimentally observed to favor tumor immune evasion [26], possibly by enabling accelerated cancer glucose consumption. LDHA has a higher affinity for pyruvate and preferentially converts pyruvate and nicotinamide adenine dinucleotide (NADH) to lactate and NAD^+ under anaerobic conditions, whereas LDHB has a higher affinity for lactate and thereby catalyzes the conversion of lactate to pyruvate. Database analyses of human melanoma patients revealed negative correlations between the expression of LDHA and T-cell activation markers. In accordance with these findings, experiments showed increased numbers of antitumor effector cells in $LDHA^{low}$ mice compared to those in the control group. By parity of reasoning, the activation and function of tumor-infiltrating immune cells (TILs), which comprise Th1 cells, NK cells, MDSCs, TAMs, CTLs, Tregs, and other immune cells, are influenced by the levels of both LDHA expression and lactic acid in the TME. Blocking LDHA or recovering the acid-base equilibrium environments in tumors may improve the efficacy of anti-programmed death-1 (PD-1) therapy [27]. However, the function of lactate anions has been relatively ignored and less studied. During an in vitro T-cell activation experiment, the addition of excess sodium lactate (NaL) enhanced the production of antitumor cytokines (such as interferon (IFN) γ, IL-2, and tumor necrosis factor (TNF)-α) more than the addition of excess sodium chloride (NaCl). This increase in cytokine production was shown to depend on TCR/CD3 activation [25].

Immunosuppressive microenvironment

High concentrations of lactate and concomitant acidification create an immunosuppressive microenvironment that limits immune cell activation and allows for immune evasion. By affecting glycolysis, oxidative phosphorylation (OXPHOS), and other metabolic signaling pathways, the distinct microenvironment changes the metabolic phenotype of immune cells, thereby impeding their normal antitumor activity. Lactic acid suppresses the proliferation and cytotoxicity of CTLs in vitro through impaired MCT1-mediated lactate and H^+ transport, resulting in the disappearance of the lactic acid gradient between the cytoplasm and extracellular space [28]. In addition, lactic acid suppresses CTL function through inhibition of p38 and JNK/c-Jun activation [29]. In natural killer T cells (NKTs), low extracellular pH inhibits NKT cell function by blocking mammalian target of rapamycin (mTOR) signaling and disturbing nuclear translocation of promyelocytic leukemia zinc finger (PLZF), thereby inhibiting IFN-γ and IL-4 production by NKT cells [30]. In contrast, Treg proliferation and function are not negatively affected by lactate, and iTreg development is favored by lactate. Tregs are less dependent on glycolysis and prefer to use OXPHOS and lipid oxidation as energy providers [31, 32]. Glucose avidity is associated with impaired functionality of Tregs because Tregs have the metabolic advantage of being invigorated by the oxidation of lactate to pyruvate mediated by LDHB; that is, Tregs can thrive on lactate as an alternative fuel. Tregs conditioned in glucose-low or glucose-deficient media upregulate the expression of LDHA and MCT1 [33], and they activate genes involved in lactate metabolism. In addition, the Treg transcription factor forkhead box P3 (Foxp3) reprograms their metabolism by suppressing Myc and glycolysis while enhancing OXPHOS and increasing NADH oxidation. Foxp3-Myc interaction can prevent endogenous lactic acid accumulation inside Tregs by favoring the oxidation of lactate to pyruvate [34]. Indoleamine 2,3-dioxygenase (IDO) is an immune regulatory enzyme expressed by Tregs that converts tryptophan to kynurenine. Upregulated Treg levels in the acidic TME also diminish tryptophan levels, which in turn stimulate stress response pathways that sustain Treg suppressive functions [35, 36]. This dominant metabolic phenotype of Tregs provides cancer cells with a chance to evade immune destruction.

Immune suppressive mediators

Tumors can survive immune surveillance by crippling CTL functionality through the production of various immunosuppressive cytokines, either from cancer cells or from non-cancerous cells present in the TME, especially those derived from immune cells and epithelial cells. Transforming growth factor-β (TGF-β) is the chief mediator among all cytokines [37]. In addition, TNF-α, colony-stimulating factor (CSF)-1, IL-1, IL-6, IL-8, IL-10, and type I IFNs can significantly contribute to tumor growth [38-42]. Protumor factors (such as CCL2, CCL5, cathepsin G, and neutrophil elastase) produced by the N2 phenotype, which is characterized by higher arginase expression level, can also induce immune suppression in the TME [43]. Lactic acid forms an inhibitory

microenvironment by regulating these mediators in the TME. For example, lactate reduces the NK cell cytotoxic response against tumor cells by decreasing the production of IFN-γ and TNF-α [26]. In mouse NK cells, IFN-γ secretion was completely inhibited at both mRNA and protein levels under 15 mM lactic acid conditions. This indicated that lactic acid alone can diminish cytokine production [26]. Moreover, tumor-derived lactate inhibits NK cell function directly as well as indirectly by promoting the development of MDSCs [44]. Under physiological conditions, bone MDSCs can differentiate into granulocytes, macrophages, and DCs. However, this process is impaired under acidic conditions, leading to the accumulation of MDSCs [45]. MDSCs have been confirmed to inhibit lymphocyte homing, stimulate other immunosuppressive cells, deplete metabolites critical for T cell function, express ectoenzymes that regulate adenosine metabolism, and produce ROS [46]. These accumulated MDSCs in both experimental and clinical tumors are considered strong contributors to the immune-suppressive TME [47]. However, NK cell effector functions can be inhibited by lactic acid and can also be reversed when acidity is buffered back to the physiological pH of 7.4, or when lactic acid generation is blocked [48].

In addition to their function, immunosuppressive mediators are also associated with the differentiation, maturation, and immune deviation of immune cells. Lactic acid is a latent inhibitor of tumor-suppressive T cells but favors the development of tumor-permissive Tregs in vitro [18, 26, 34]. Lactate can even drive T cells toward an immunosuppressive Treg phenotype [34]. A similar phenomenon also occurs in macrophages, where the antitumor pro-inflammatory M1 phenotype has high glucose consumption, whereas the protumor M2 phenotype does not, consuming either lactate or fatty acids [49]. Intrinsically, lactic acid consumed by macrophages upregulates the neovascularization factor vascular endothelial growth factor (VEGF), and the M2-marker arginase 1 (Arg1) [50, 51]. TME acidity has a direct effect on macrophage phenotypic polarization, skewing their differentiation toward the immunosuppressive M2 phenotype through ERK/STAT3 signaling activation [51], and stimulating the secretion of CCL5 through activation of Notch signaling in macrophages [52, 53]. After recognizing CCR5, which is regulated by TGF-β signaling in breast cancer cells, CCL5 increases cell migration, induces epithelial-mesenchymal transition (EMT) in cancer cells, and promotes aerobic glycolysis in cancer cells by mediating AMPK signaling [54]. In addition, the ability of lactic acid to mediate M2 redistribution is also dependent on HIF-1α stabilization to some extent [55]. Like in macrophages, lactic acid promotes an alternative N2 functional profile in neutrophils, which is characterized by poor phagocytic ability and suppressed ROS production [56]. N2-tumor associated neutrophils (TANs) express high levels of CD11b/CD18 and β2 integrin, and they contribute to tumor growth and metastasis through multiple pathways, including the production of angiogenic factors, suppression of T cells, and secretion of proteases (such as MMP-9 and elastase) [56]. DC precursors do not express CD1a and are incapable of differentiating into DCs when cultured with IL-4 and GM-CSF derived from different tumor cell lines [14]. In addition, monocyte-derived DCs (MoDCs) developed using low cell density cultures have a superior ability to produce inflammatory cytokines, migrate toward lymphoid tissue guided by chemokine CCL19, and induce Th1 polarization. Conversely, MoDCs originating from dense culture do not produce inflammatory cytokines upon activation but secrete IL-10. This cell concentration-dependent pathway acts through lactic acid, which builds up in dense culture and induces early and long-lasting reprogramming of MoDC differentiation [57]. The differentiation deviation of these immune cells can be reacquired upon pH reversal. In addition to cytokines, other immunosuppressive factors such as VEGF secretion by tumors also hamper the differentiation of progenitors into DCs [58]. Therefore, lactic acid serves as a critical immunoregulatory molecule that influences immune cell differentiation. The role of lactate as an epigenetic regulator through histone modification has also been considered. By directly combining histone lysine acetylation sites, lactate initiates the expression of many genes in various immune cells. For example, lactic acid stimulates the expression of traditional genes associated with M2 macrophages [50, 51]. The ability of macrophages to polarize into the M2 phenotype through lactic acid-induced acidosis in the TME is likely due to histone lysine acetylation and subsequent enhanced inflammation-independent biological pathways [59]. This may explain the dedifferentiation and loss of anticancer abilities of multiple cell types in an acidic extracellular environment. However, considering lactic acid as a general epigenetic regulator still requires greater understanding and a more comprehensive acceptance of its profound role in tumor biology, especially in shaping anticancer immunity.

Angiogenesis

Angiogenesis factors drive immune escape by directly inhibiting APCs as well as immune cells and indirectly by augmenting the effects of Tregs, MDSCs, and TAMs. These immunosuppressive cells can also stimulate angiogenesis, forming a vicious cycle of impaired anti-tumor immunity [19]. VEGF inhibits the activation of nuclear factor kappa B (NF-kB) [60], differentiation, and antigen presentation of APCs [61], while increasing their PD-L1 expression level [62]. VEGF also suppresses the differentiation, proliferation, and cytotoxicity of T cells

[28] and accelerates T cell exhaustion by increasing the expression levels of checkpoints such as PD-L1, CTLA-4, lymphocyte activation gene 3 (LAG3), and TIM3 [29]. Angiogenesis driven by another angiogenic factor, angiopoietin-2 (Ang-2), is distinct from that induced by VEGF. Ang-2 increases the recruitment and adhesion of both neutrophils and Tie-2–expressing monocytes (TEMs) to the endothelium [58] and then contributes to the preference for conversion to M2 macrophages [50]. However, unlike VEGF, Ang-2 does not directly affect T cells, but can indirectly contribute to the expansion of Tregs and the suppression of effector T cells by promoting TEMs to secrete IL-10 [50, 58]. Furthermore, MDSCs can initiate the formation of a pre-metastatic niche by increasing angiogenesis and enhancing tumor cell stemness [63].

An acidic pH is required for the expression of lactate-induced VEGF [52]. Exposure to lactate enables the metabolic utilization of lactate by macrophages with LDHB-catalyzed conversion of NAD^+ to NADH, which reduces the cellular NAD^+ pool and subsequently unchecks the suppressive responses mediated by NAD^+-dependent ADP-ribose polymerase. This metabolic phenomenon has been shown to promote the synthesis of VEGF by macrophages and induce angiogenesis at the wound and tumor sites [16]. The efflux and influx of lactate in the lactate shuttle of vascular endothelial cells is mediated by MCT4 and MCT1, respectively. After being imported into the cells, lactate is oxidized to pyruvate, which initiates NF-κB/IL-8 signaling and stabilizes HIF-1α by preventing HIF-1α prolyl hydroxylation. Therefore, increased lactic acid production and the subsequent acidic environment and HIF-1α overexpression co-induce vasculogenesis and angiogenesis through the VEGF pathway also under normoxic conditions [20].

Tolerance

Inhibitory molecules, death signals, and apoptotic signals are all significant contributors to cancer immune escape by promoting undue immune tolerance against tumor cells through enervating and depleting effector cells.

Inhibitory molecules

PD-1 is an inhibitory molecule expressed mainly by activated T cells on the cell surface and serves as a negative regulator of antitumor immune responses by dephosphorylating TCR. In the acidic TME, MDSCs increase their activity through the acid-induced HIF-1α pathway, resulting in augmented PD-L1 expression and myeloid cell death [64]. Lactic acid is a pivotal inhibitory signaling molecule that plays a key role in cancer cell growth, angiogenesis, immune escape, migration, and invasion [65]. This signaling molecule function depends, at least partially, on its binding to lactic acid receptors. By activating G protein-coupled receptor 81 (GPR81) on cancer cells, lactic acid enhances tumor cell proliferation, drug resistance, and PD-L1 expression through an autocrine pathway [66–68]. In a paracrine manner, cancer cell-derived lactate activates GPR81 in endothelial cells, immune cells, and adipocytes present in the TME. Activation of GPR81 on DCs triggers downstream cascades, such as decreased generation of cyclic adenosine monophosphate (cAMP), IL-6, and IL-12, suggesting that paracrine lactic acid signaling to DCs inhibits the presentation of tumor-specific antigens to T cells [69]. In addition, GPR81 knockdown mice exhibited suppressed Treg generation [70]. Therefore, the end results of GPR81 activation promotes angiogenesis, immune escape, and chemoresistance. Migratory inhibition factor (MIF) is an emerging immunosuppressive factor. Blocking MIF-CD74 signaling reduces lactate production, as well as HIF-1α and PD-L1 expression levels in resistant cancer cells, potentiating $CD8^+$ T cell infiltration and driving macrophage conversion toward the pro-inflammatory M1 phenotype [71].

Immune cell depletion

Depleting immune cells is another approach used by cancer cells to escape immunity. Lactate can reduce immune cells in several ways, such as impeding their proliferation, promoting apoptosis, and reducing their accumulation in the TME. Tregs tend to accumulate in the acidic TME; therefore, they are increasingly being evaluated as immune therapeutic targets [176]. However, in other immune cells, the serum lactate level is negatively related to the number of effector immune cells and positively associated with tumor burden in cancer patients [161]. Upon activation, T cells (excluding Tregs) in the TME change to a cancer-like Warburg metabolic phenotype and produce more lactic acid, which theoretically supports the rapid proliferation of the cancer cells. However, monocarboxylates and H^+ bidirectional symport by MCT-1 require a lactic acid concentration gradient between the cytoplasm and extracellular space. Consequently, MCT transporters cannot function optimally, thereby disturbing intracellular pH homeostasis in activated T cells, or the resultant intracellular acidification directly kills the cells. Lactate concentrations above 20 mM can invalidate the cytotoxic activity of CTLs and NK cells by causing apoptosis through blocking the FAK family interacting protein of the 200 kDa pathway both in vitro and in vivo [13]. Lactic acid can also induce NK cell apoptosis through mitochondrial dysfunction by decreasing the intracellular pH, which can be prevented by inhibiting mitochondrial ROS accumulation [5]. A decreased intracellular PH also expedites neutrophil

apoptosis. The key regulators of apoptosis, such as caspase 3, also have reduced activation under such conditions [74]. With respect to cell accumulation, upon the influx of lactic acid through the SMCT2 transporter, either decreased phosphofructokinase or downregulated hexokinase 1 of Ths and CTLs can result in the inhibition of glycolysis, and finally, the reduction of cell motility [75]. As such, these effector cells lose responsiveness to chemokines and no longer infiltrate areas of the body, resulting in less accumulation in the TME. In contrast, resisting committed cell death, that is, evading apoptosis, is also thought to be a hallmark of cancer and represents an important mechanism in tumor resistance to oncological therapies [37, 40]. LDHA plays a role in reducing the apoptosis of tumor cells. Lack of LDHA enhances oxygen consumption, resulting in elevated levels of mitochondrial ROS (mROS) [38, 39, 41]. As ROS are powerful stimulators of $Ca2^+$ internalization, knocking down LDHA leads to increased intracellular levels of $Ca2^+$, which triggers apoptosis by activating apoptotic endonucleases [26, 43].

Lactate is not an innocuous bystander or waste metabolite. In essence, lactate exported by glycolysis-dependent hypoxic cancer cells, which cannot oxidize lactate, is taken in by neighboring normoxic cancer cells to synthesize ATP through mitochondrial respiration [76]. However, the limited direct measurements of lactate in the interstitial fluid suggest relatively modest accumulation, which is substantially lower than the levels used in the culture fluid of in vitro cell studies. The gradient between incoming and outgoing blood measurements revealed that some tumors consumed lactate. The uptake of circulating lactate is oxidized to pyruvate and serves as a tricarboxylic acid (TCA) intermediate [77–79]. Because the material exchange between tumor cells and circulation is so rapid, little pyruvate generated from glucose through the upregulated glycolysis of the tumor is involved directly in the TCA cycle. Instead, tumor-derived pyruvate is mostly converted into lactate and excreted, with most of the TCA ingredient pyruvate in the tumor coming from circulating lactate produced elsewhere in the body [79]. In summary, we need to characterize the tumor metabolic milieu more precisely, which is particularly critical because of the marked metabolic composition difference between the microenvironment and the tumor mass due to active transport processes. Direct interstitial fluid sampling and subsequent metabolomic analysis may be feasible steps in this regard. The overall mechanism network of lactate acid is showed as below (Fig.1).

Adenosine

Adenosine is an immunosuppressive end-metabolite produced at high levels within the TME, where its precursor, ATP, is abundantly released into the extracellular space in response to cell death signals, cell stress, and opening of pannexin/connexin channels on immune or endothelial cells [80, 81]. Ectonucleotidases (most prominently CD39 and CD73) favor the degradation of ATP into adenosine and thus disrupt antitumor immunity [82, 83]. CD39 and CD73 are ubiquitously expressed in various cells within the TME, including tumor, stromal, immune, and endothelial cells [84]. Exosomes derived from $CD39^+CD73^+$ tumor cells, Tregs, and mesenchymal stem cells can also generate adenosine [85]. CD39 and CD73 successively catalyze ATP to AMP and AMP to adenosine. Overexpression of CD73 in the TME reverses the immune-activating role of ATP, suppressing adenosine and promoting tumor growth. CD73 expressed on the surface of tumor cells is one of the reasons for tumor immune escape, and inhibition of CD73 may reinvigorate the activity of T cells and enhance the antitumor immune monitoring ability of immune cells decreased by adenosine. Immunosuppressive subpopulations, including Tregs and MDSCs, in both the tumor mass and lymph nodes, also upregulate CD73/CD39 expression, thereby enhancing their intrinsic immunosuppressive effect [86]. Hypoxia, which is a common phenomenon in many cancers, has also been verified as one of the main stimulators for the buildup of extracellular adenosine [87]. Adenosine can locally stimulate four subtypes of specific G protein-coupled receptors (A1, A2a, A2b, and A3) [88]. Among these, only activated A2a and A2b receptors on immune cells can trigger strong immunosuppressive responses. Upon engagement of either A2a or A2b receptors, adenosine induces increased adenylyl cyclase activity with concomitant increased generation of intracellular cAMP [89] and subsequent activation of protein kinase A (PKA) [90-96]. cAMP plays a suppressive role through cAMP/PKA-mediated blocking of the TCR, NF-kB, and Janus kinase-signal transducer and activator of transcription (JAK-STAT) signaling pathways [97]. In addition, in vitro assays using mouse and human T cells have consistently confirmed that both Ths and CTLs rapidly upregulate A2a following TCR activation in an NFAT-dependent manner [98]. As for myeloid cells, particularly TAMs, A2a expression also indirectly contributes to the suppression of antitumor immunity by suppressing $CD8^+$ T and NK cells [99]. Tregs are a significant source of adenosine in the TME; however, they can also respond to autocrine/paracrine adenosine stimulation by expressing adenosine receptors. In support of a direct promoting role for A2b signaling in Tregs, a previous study demonstrated a strong increase in A2b mRNA expression level in Tregs following TCR activation [100].

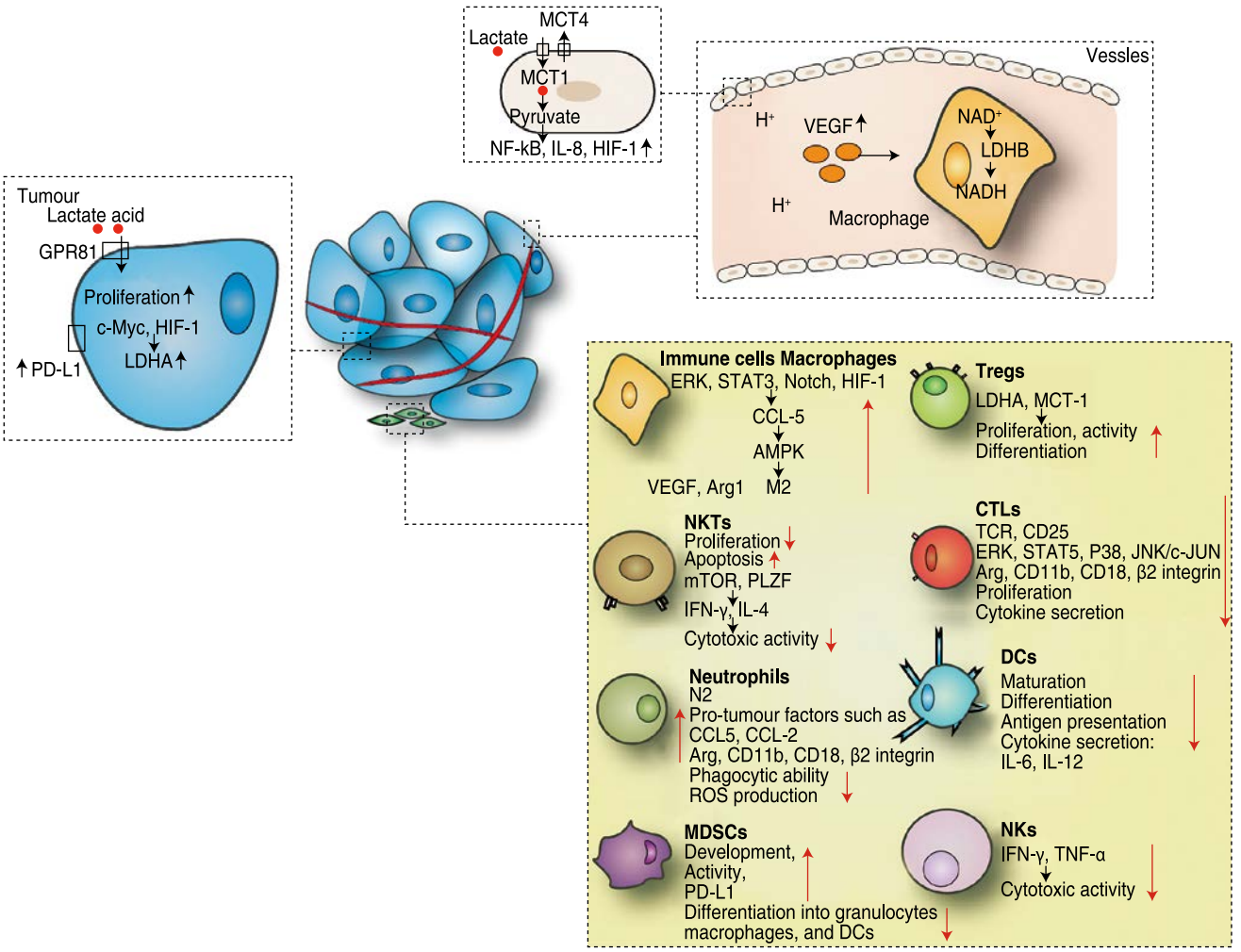

Fig. 1 The interaction between lactate acid and tumour immune escape. Lactate acid promotes tumour cells' immune escape by inducing immune cells to differentiate into immunosuppressive phenotypes and then secreting immune-suppressive mediators. The proliferating effects of lactate acid applied to tumour cells and vascular epithelial cells also contribute to the immune escape

Immunogenicity

Presentation

Depending on A2b signaling, adenosine skews aberrant differentiation of monocytes to DCs, deviating them toward a Th2-helping, pro-angiogenic, and tolerogenic phenotype characterized by the production of IL-6, IL-8, IL-10, and VEGF, as well as the expression of immunosuppressive markers such as TGF-β, IDO, Arg2, and cyclooxygenase (COX2) [101]. Blocking A2b receptors promotes DCs activation and the subsequent CXCR3-dependent antitumor responses [102]. Therefore, adenosine has been proven to diminish the capacity of DCs to prime and amplify Th1 immune responses by activating the CD39, CD73, and A2b receptors.

Recognition

Adenosine impairs antigen recognition and subsequent T cell activation. Increased PKA activity secondary to A2a receptor signaling in effector T cells has additional suppressive effects, including attenuation of proximal TCR signaling by inhibiting the LCK-dependent activation of ZAP70 [103, 104] and protein kinase C activity, which is critical for effector cell activation [105]. A2a receptor signaling in $CD4^+$ Ths decreases IL-2 secretion, which reduces the expression level of the costimulatory receptor CD28 [106].

Immunosuppressive microenvironment

Through the A2 receptor, adenosine creates an environment that facilitates the reduction of immunosurveillance cells, while favoring the expansion of immunosuppressive cells. A2b stimulation is beneficial

for the differentiation and proliferation of $CD11b^+ Gr1^{high}$ neutrophilic-like MDSCs characterized by high levels of CD73, thereby potentiating adenosine-mediated immunosuppressive functions [107]. In addition, A2a activation ultimately leads to decreased T cell expansion and activation [98, 100] and the rise of profound T cell anergy [98, 108].

Immune suppressive mediators

Inhibiting the mitogen-activated protein kinase (MAPK) pathway through ERK1 and JNK and promoting TNF-α secretion, A2a activation induces transcription of the c-Jun/AP-1 complex in activated T cells and stimulates the formation of $LAG3^+$ Tregs by inducing TGF-β secretion [98]. Adenosine production by Tregs through CD39 and CD73 expression reinforces anergic properties related to their function through autocrine A2a receptor signaling. To this end, A2a receptor agonism results in Treg expansion and can be adoptively transferred before ischemia-reperfusion injury to enhance the protective capacity [109-111]. Stimulation of the A2a receptor on naive $CD4^+$ T cells also promotes the development of Tregs by activating and increasing Foxp3 and LAG3 synthesis [112]. This is the effect of adenosine on the proliferation of immune cells.

As for immune cell functions, in murine models, studies have found that metastasis of $CD73^+$ tumor cells is associated with A2a/cAMP/PKA-mediated suppression of NK cell anti-tumor activities in a manner of decreased perforin and IFN-γ production [113, 114]. The downstream mTORC1 pathway functions as the main axis for adenosine-mediated impairment of T cell function and metabolic fitness [115]. In addition, the A2a/cAMP/PKA pathway results in the inhibition of pro-inflammatory NF-kB signaling [100]. Accordingly, A2a activation in T cells has been shown to increase the secretion levels of TGFβ, IL-10, PD-1, and LAG-3, as well as decrease the levels of pro-inflammatory cytokines, such as IFN-γ, TNF-α, and IL-6 in vivo and in vitro [93, 98, 100]. In the TME, tumor-associated endothelial cell (TEC)-derived CD73 can produce adenosine that downregulates ICAM-1, thereby repressing the adhesion and the transmigration of antitumor T cells [96]. Thus, adenosine signaling in TECs hinders T cell homing to tumors. Changes in B cell functionality have also been reported due to alterations in T cells within germinal centers [116, 117]. CD39, CD73, and A2a receptor expression on B cells also suppresses effector T cell functions and impairs the secretion of immunoglobulin (Ig)A- and IgG-type antibodies.

Adenosine also affects immune cell differentiation. TGF-β mediates the maturation of MDSCs into tumor-associated terminally differentiated myeloid mononuclear cells, which exhibit high levels of CD39/CD73 expression and adenosine-generating capacity [118]. A2a-deficient TAMs, in sharp contrast to A2a-proficient TAMs, display characteristics similar to antitumor M1, which possesses increased MHC II and IL-12 levels while decreasing IL-10 expression level. Through A2a and A2b receptor signaling, TAMs are stimulated to secrete IL-13 and IL-4, thereby increasing Arg level that inclines TAMs to initiate M2 activation and inhibit $CD4^+$ T cells.

Angiogenesis

In A2a receptor-deficient mice, tumor angiogenesis was decreased, and the subsequent starvation of tumor cells ultimately caused their death [94, 119]. Similarly, A2b receptor activation in MDSCs induces VEGF secretion and angiogenesis. Global loss of CD39/CD73 or A2a/A2b receptors resulted in decreased VEGF and CD31 (also known as PECAM1) staining of tumor vessels in mouse models [120-123]. CD73 has pro-angiogenic effects through both enzymatic and non-enzymatic pathways, which was confirmed by reduced tumor levels of VEGF and suppressed tumor angiogenesis in a breast cancer mouse model after treatment with a monoclonal antibody targeting CD73 [120].

Tolerance

Inhibitory molecules and immune cell depletion

A2a receptor signaling of both effector and regulatory T cells triggers the upregulated expression of immune checkpoint molecules, including PD-1, CTLA-4, and LAG-3 [105, 120, 124, 125]. In addition, the tumor suppression induced by A2a receptor antagonism may function through $CD8^+$ T cells and the release of cytotoxic granules as well as FAS ligand ligation with the death receptor FAS (also known as CD95) of tumor cells [113, 119]. However, there are no relevant studies on the effects of adenosine on immune cells and tumor cell apoptosis in the TME. The overall mechanism network of adenosine acid is showed as below (Fig.2).

ROS

ROS are mainly present as by-products of the OXPHOS system or in specific enzymatic reactions (such as nicotinamide adenine dinucleotide phosphate oxidase and dual oxidase), which have two faces depending on their balance in the TME. Therefore, ROS homeostasis is rigorously regulated by antioxidative machinery comprising superoxide dismutase, catalase, and glutathione peroxidase. ROS are produced not only by tumor cells but also by cellular components that make up the TME. MDSCs are often a major source of ROS in TME. In addition to their release of oxidizing species, MDSC levels often arise in oxidative stress-prone environments, such as tumors. ROS and nitric oxide are responsible for multiple

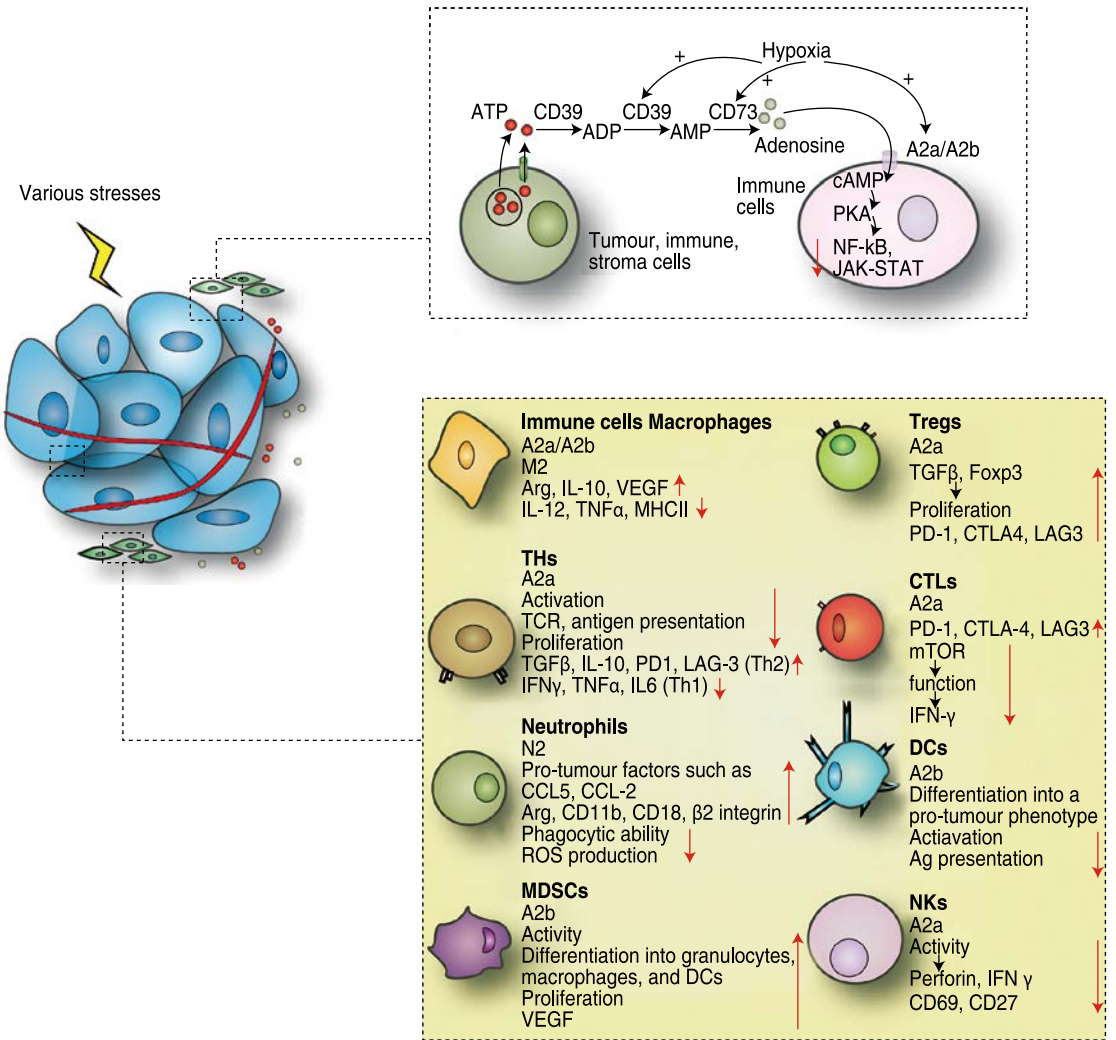

Fig. 2 The interaction between adenosine and tumour immune escape. Increased adenosine in responses to various stresses disrupts anti-tumour immunity through the A2a/A2b – cAMP – PKA pathway in many immune cells. The detailed influences can also conclude to differentiation, decreased tumour cytotoxicity, and increased immunosuppressive capacity

immune regulation responses related to tumor immune evasion; however, the differing effects on biological functions correspond to the amount of ROS. Although high levels of ROS can cause cytotoxic damage and cell death in tissues, as well as cause immune deregulation, their low cytostatic levels can have a proliferative effect that benefits tumor growth and the maintenance of biological processes. That is, ROS maximize the role of tumor promotion when ROS levels reach super-physiological or cytostatic levels, while avoiding too high levels to be conducive to cell death. Notably, ROS may be major stimulators of immunosuppression. Therefore, ROS are not only inducers of oxidative stress, but also mediators of immune regulation within the TME and are important in promoting tumorigenesis.

Immunogenicity

Presentation

In the context of cancer cells, the free oxygen radicals produced in the inflammatory TME can cause alterations in the cellular oxidative state as well as post-translational modifications of cysteine residues in proteins [126], which may alter antigenicity and contribute to T cell immunity. The redox status of antigens can modify the affinity of TCR for the antigenic peptide [127, 128]. Moreover, ROS-induced oxidative stress triggers the generation of upregulated antigenic peptides, which are counteracted by the limitation of their capacity to be loaded onto MHC molecules [129]. DCs impede antigen presentation due to chronic ER stress responses and cause oxidative damage to intracellular lipids because of excessive ROS [130, 131].

Recognition

Modest production of ROS by cancer cells can induce hypoxia [132], which can regulate T and NK cell immunity by modulating their activation through the expression of costimulatory (CD137 and OX-40) and coinhibitory (PD-L1) molecules [133]. In addition, senescent myeloma cells enhanced ligands (MICA, MICB, and PVR) to strengthen NK cell activation through NK cell activating receptors, such as natural killer group 2 member D (NKG2D) and DNAX accessory molecule-1 (DNAM1), both in an oxidant-dependent manner [39]. Moreover, upregulated gene expression of MICA and MICB was also observed in the CaCo-2 colon carcinoma cell line after oxidative stress [135], a phenomenon that could strengthen NK cell recognition and promote tumor cell elimination.

Immunosuppressive microenvironment

TILs all have decreased infiltration and cytotoxic activity [136] and embrace a differentiation skewing toward protumor type 2 as well as increased anergy [137] and apoptosis [138] in the context of ROS. ROS and oxidative stress in the TME help drive tumors to escape immunity, mainly through their effects on TILs. A high level of ROS in the TME inhibits T cell proliferation and antitumor function. Alternatively, low levels of ROS are required for T cells activation, proliferation, and function [139, 140]. ROS also affect the function of TILs, depending on the level of mROS. In renal clear cell carcinoma, $CD8^+$ TILs were present but with impaired function and metabolism. This effect was rescued by MitoQ and MitoTEMPO, both mROS scavengers, as evidenced by enhanced $CD8^+$ TILs activation [141]. Furthermore, ROS generated by other cells within the TME lead to T cell hyporesponsiveness in cancer patients [142]. The lipid raft-associated protein caveolin-1 (CAV-1) negatively regulates exosome internalization [143]. Studies have demonstrated a possible pathway by which tumor cells generate ROS, which signals to fibroblasts and causes the degradation of CAV-1, thereby increasing exosome influx. Zhao *et al*. suggested that exosomes isolated from prostate and pancreatic cancer-associated fibroblasts (CAFs) contain high amounts of lactate, glutamine, acetate, various amino acids, and many other metabolites, suggesting a potential role for exosomes in anaplerosis and lipogenesis [144]. The effect of increased exosome influx can lead to increased uptake of metabolites and metabolic reprogramming of fibroblasts to more tumorigenic CAFs, such as myofibroblasts [145, 146]. Macrophage-derived ROS affect Treg function [147]. When collaborating with large amounts of released ATP and adenosine, which are immunosuppressive, ROS and oxidative stress in the TME leads to more potent immunosuppression through Tregs [148].

Immune suppressive mediators

ROS-affected immunoregulatory factors in the TME play their role by influencing immune cell function, proliferation, and differentiation. TAMs amplify their infiltration and ROS production and promote Treg recruitment in the TME, which is ascribed to their proven high antioxidative capacity [45, 149]. And TAMs skew toward M2 is likely due to ROS-dependent TNF-α secretion [150]. TANs enhance ROS production and induce oxidative stress, which strengthens the suppression toward lymphocytes, such as inhibiting the proliferation of $IL17^+$ T cells [151] and restraining murine NK cell activity against tumor cells [152]. Tregs also exhibit increased accumulation and immunosuppression in the presence of ROS. Consistently, Kunisada *et al*. reported that metformin decreased the number of tumor-infiltrating Tregs by inhibiting the differentiation of naïve $CD4^+$ T cells into Tregs through Foxp3 protein [118]. Furthermore, metformin evokes metabolic reprogramming of Tregs toward a more glycolytic state [153]. Therefore, by reducing the levels of mROS with mitochondrial-targeted antioxidants, such as metformin, Tregs may become less immunosuppressive, allowing for an upregulated CTLs tumoricidal effect. Surrounded by ROS, MDSCs maintain their phenotype in the undifferentiated state [154, 155], have stronger immunosuppression abilities with attenuated recognition between TCR and MHC-peptide complex [156], exhaust arginine and cysteine, and generate peroxynitrite. Moreover, MDSCs also upregulate the ROS-producing enzyme COX-2 in T cells [157, 160], and through the produced ROS, tumor-induced MDSCs suppress T cell proliferation to promote colorectal cancer cell growth [123]. In support of these findings, the immunosuppressive effects of MDSCs on T cells was shown to be completely abrogated by ROS inhibitors [161, 162]. Finally, although high levels of ROS are immunosuppressive, a low level of ROS is important for T cells activation [163]. Low levels of ROS in CTLs have an anti-tumorigenic effect, but high levels of ROS in Tregs appear to be linked to reduced immunosuppression. ROS are required to induce a more locally invasive phenotype in TAMs isolated from melanoma, and this effect was regulated through ROS-dependent TNF-α secretion [164]. Taken together, this illustrates that the level of ROS within a certain cell type has different consequences for the function of that specific cell. Furthermore, similar levels of ROS can also have contradictory effects on various cell types. As shown previously, in $CD8^+$ TILs isolated from renal clear cell carcinoma, high levels of ROS resulted in impairment and even lack of antitumor response, while high levels of ROS in TILs in colon carcinoma from mice treated with anti-PD-1 blockade were related to increased tumoricidal effects.

Further research into how ROS within TILs and extracellular ROS involvement in modulating tumor

immunity will be needed to better characterize how different concentrations, types of ROS, and locations affect tumor immunity. Interestingly, healthy cells have evolved adequate adaptations to overcome the damaging protumor effects of ROS. Balanced production of ROS, sufficient antioxidant storage, and thorough cellular repair lead to low concentrations of ROS, resulting in limited tumor cell survival and proliferation. Maintenance of tumor cell metabolic activity results in high ROS levels, leading to DNA damage, genetic instability, and decreased cellular repair through functional DNA damage repair pathways. Elevated ROS levels can induce cellular damage, but tumor cells also readjust with sufficient adaptations, including hypoxia, as well as through initiation of an alternative cellular repair mechanism. Tumor cells express an elevated antioxidant capacity to remove excessive ROS while maintaining protumorigenic signaling. However, if ROS concentrations increase dramatically and approach toxic ROS levels, for example, by employing ROS-inducing agents such as chemotherapy, the resulting oxidative stress causes irreparable damage, inadequate adaptation, and eventual tumor cell death.

Angiogenesis

ROS derived from NOX and mitochondria play a pivotal role in the angiogenic transition from quiescent endothelial cells (ECs). In adults, ROS are augmented in response to growth factors (such as VEGF), ischemia, and wound injury, which promote the angiogenic switch in ECs. Excess ROS contribute to pathological angiogenesis in cancer. Exogenous ROS increase VEGF and VEGFR2 expression levels [165] and stimulates ECs proliferation and migration [166, 167]. Interestingly, VEGF-induced ROS determine VEGFR2 tyrosine phosphorylation, which is a prerequisite for ECs migration and proliferation through stimulation of small GTPase ARF6 residing in caveolae/ lipid rafts in ECs [168]. Furthermore, ROS-mediated redox signaling associated with angiogenesis involves MAPKs, PI3 kinase, JAK-STAT, Akt, protein tyrosine phosphatases (PTPs) such as PTP1B, SH2-containing protein tyrosine phosphatase 2, phosphatase, and tensin homolog, as well as transcription factors, including HIF-1, AP-1, and NF-kB. Mitochondria function as an O_2 sensor that transmits a hypoxic signal by releasing ROS to the cytosol [169]. Hypoxia stimulates mROS production from mitochondrial complex III, and the mROS trigger HIF-1α stabilization [167-172], which enhances the transcription of angiogenic genes such as VEGF [172].

Tolerance

Inhibitory molecules

Although no direct and specific relationship has yet been deduced between elevation or reduction of ROS production and regulation of coinhibitory PD-L1 expression, ROS have been shown to affect the expression of PD-L1 in cancer cells in vitro [173]. Lower levels of global ROS as well as hypoxia in the TME coupled with increased intracellular mROS in specific tumor-infiltrating cells may induce the most efficacious reaction to PD-1 blockade [141, 174].

Tumor cell depletion

One of the most crucial advances in cancer research in recent years has been the recognition that tumor cell death, mostly through apoptosis, is strongly linked to the regulation of tumor formation and the critical determination of treatment efficacy. Therefore, we believe that avoiding effector immune cell-induced apoptosis can also be attributed to the manner in which tumor cells evade antitumor immunity. The killing of tumor cells, as in most anticancer strategies currently used in clinical oncology, is linked to the intrinsic (intrinsic apoptotic signal in the mitochondria) or extrinsic (extrinsic apoptotic signal by death receptors) pathway of activation of apoptosis signal transduction in cancer cells. Thus, successful apoptosis may result in reduced resistance to treatment. Binding of the TNF-α ligand to the death receptor TNFR1 induces the stimulation of initiator caspase 8, leading to the cleavage of caspase 3 [175]. Caspase 8 activation also triggers the cleavage of Bid to tBid, resulting in the release of cytochrome C in an intrinsic apoptotic pathway [176]. Toxic levels of ROS damage the mitochondrial membrane, causing the release and translocation of cytochrome C into the cytoplasm. Then, by binding with Apaf-1 and pro-caspase 9, cytochrome C forms a complex that induces the cleavage of caspase 3 and caspase 7, which finally results in apoptosis [177]. The overall mechanism network of ROS is showed as below (Fig. 3).

Conclusions

This review emphasizes that a deeper understanding of the effects of tumor metabolism and metabolite on tumors may advance the frontier of immunotherapeutic approaches. The specific focus of this work was on the three well studied end-metabolites and their roles in tumor immune escape. These end-metabolites impact the immune responses from antigen presentation and antigen recognition, to the activation, proliferation, and function of effector cells, and they are effective from the very early stages of tumor formation to local invasion and distant metastasis. Other non-immune cell activities and

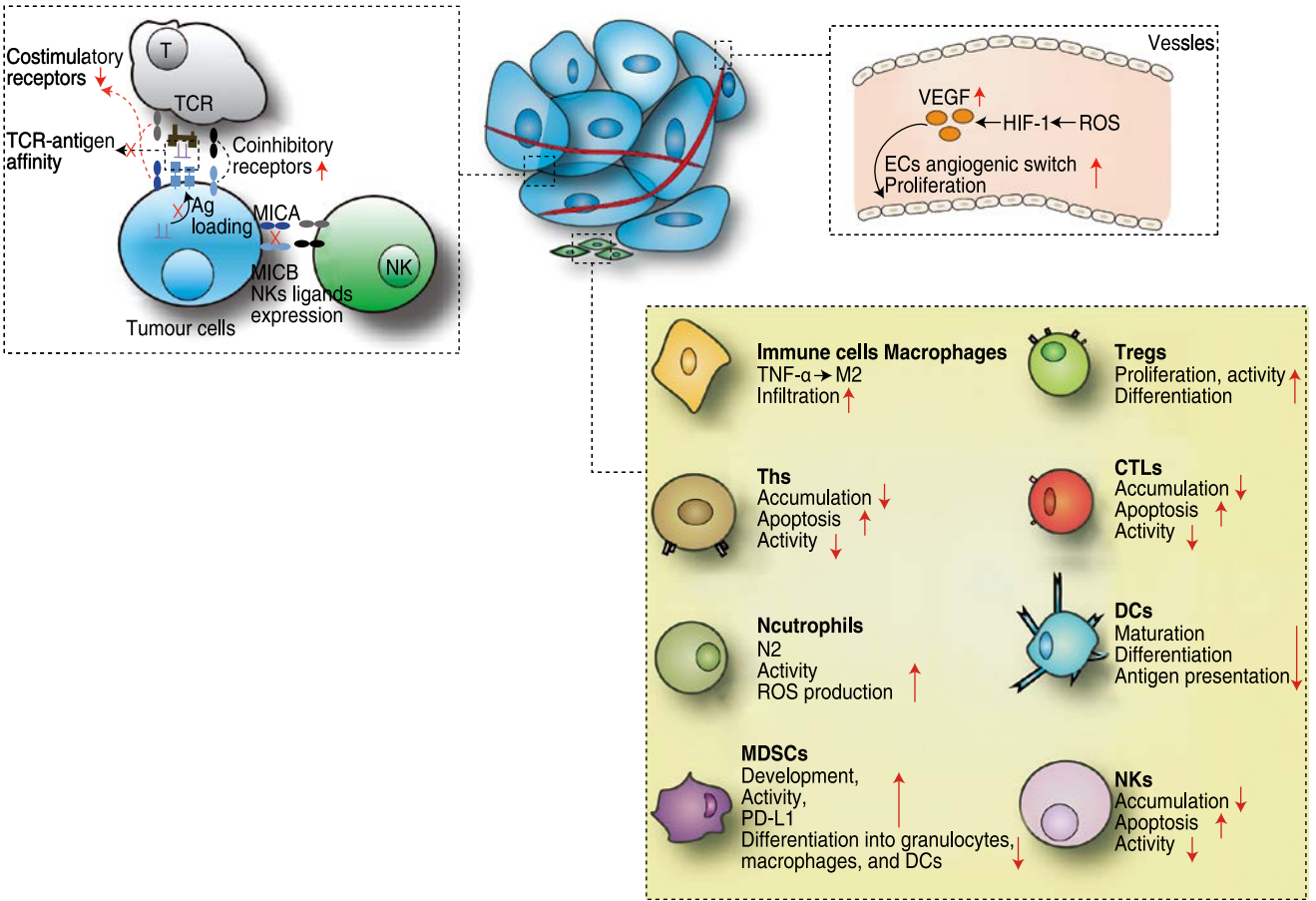

Fig. 3 The interaction between ROS and tumour immune escape. ROS impedes immunological surveillance and immune clearance by weakening the activation of tumour killer cells. Besides, ROS has the same infection on immune cells and angiogenesis as lactate acid

angiogenesis in the TME also changed in response to these metabolites. Regarding the overall interaction, there are many potential drug targets, some of which have been discovered, and corresponding drugs have been designed, which are undergoing animal or clinical trials. Some targets need to be evaluated further. However, it is not yet clear whether these three end-metabolites promote other immune escape mechanisms found in some tumors, such as (1) the silencing, loss, or mutation of related fragments in the tumor cell genome and epigenetic modifications such as RNA interference that inhibit antigen transcription and antigen presentation or promote antigen degradation; (2) the decrease of the release of tumor danger signals by tumor cells through MerTK-dependent cell burial; (3) the production of miR-214 by tumor cells, which is injected into nearby T cells through microbubbles, mediating the expansion of Tregs and causing immunosuppression; and (4) the independent production of mitotic signals and growth factors by tumor cells, which increases genetic instability to accelerate evolution and fast adaptation to the immune environment. Other end-metabolites, such as NO, bile acids, bilirubin, and uric acid, also require further exploration to assess their association with the tumor immune escape. An in-depth understanding of how tumors evade immune surveillance fueled by these end-metabolites will help researchers elucidate the essence of tumor occurrence and development as well as develop more effective therapeutic strategies.

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Conflicts of interest

The authors indicated no potential conflicts of interest.

Author contributions

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Data availability statement

Not applicable.

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