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Review

Major fundamental factors hindering immune system in defense against tumor cells: The link between insufficiency of innate immune responses, metabolism, and neurotransmitters with effector immune cells disability

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ABSTRACT

Despite the major progresses in comprehending the mechanisms of tumor immunosurveillance and the role of innate and adaptive immune systems in recent years, there are still a number of obstacles hindering successful and effective immunotherapy of cancer. Such obstacles have been mainly attributed to the ability of tumors in creating a tolerant microenvironment and exploiting a plethora of immunosuppressive factors that counter effective immune responses against tumor cells. Here we represent a new insight into probable links between immune system disability with metabolism and chronic psychological stress which is beyond the other strategies recruited by tumors to thwart tumor immunosurveillance. In addition, we underscore the prominent role of improper innate immune responses as one of the underlying causes of either pro-tumorigenic capability or tumor immunosurveillance failure. However the insufficiency of stimulatory factors in immune responses is a major fact leading to tumor survival, metabolic suppression of immune cells in tumor microenvironment, as well as the negative influences of chronic stress and depression in cancer patients are important parameters amplifying disability of immune responses which have mostly been underestimated in cancer immunotherapy. Stress-related catecholamines are suggested as immunosuppressive factors. In addition, tumor cells have distinct metabolic pathways and secrete various metabolites in the tumor microenvironment which may inhibit T cells activity. We believe that simultaneous control of metabolic and psychological negative influences on the tumor immunosurveillance, along with addressing the weak aspects of innate and adaptive immune responses in cancer immunotherapy may result in more successful treatment of tumors.

1. Introduction

Cancer is a detrimental disease which emanates from mutant sequences of DNA that shifts crucial pathways interfering cell death/survival and tissue homeostasis. The worldwide prevalence of cancer is steadily increasing and it was predicted that the number of newly diagnosed cancer patients will approach to 15 million cases by 2020 leading to the death of roughly 12 million people per year, but recent statistic data indicates that the number of newly diagnosed cancers have been surpassed 18.1 million cases in 2018. While cancer is mainly attributed to DNA mutation and genetic disorders, other factors such as diet, lack of exercise, alcohol, tobacco, industrial exposures, inflammation, and infectious diseases are considered as the notable risk factors associated with the development of cancer [1,2].

The term “cancer immunosurveillance” was first used in the early twentieth century when Paul Ehrlich postulated that immune system could repress the growth of carcinomas. After decades, now experimental evidence indicate that development and progression of cancers is highly dependent on immune responses [3,4]. Different antigens capable of being recognized by the host immune cells are found on the cancer cells including fetal antigens, overexpressed self-proteins and in most cases point mutations of normal genes favor the development of neoepitopes; nonetheless, tumor expansion observed in most cases implies that the tumor cells are capable of escaping the immune responses. Despite the abundance of immunogenic antigens in many cancers, the immune-mediated tumor cells destruction is generally inefficient in most patients [5].

In recent years, immunotherapy has revolutionized the era of cancer treatment through modulating immune responses against cancers, obviating the shortcomings of highly morbid and inadequate therapies like chemo and radiotherapy [6]. Reinforcement and recruitment of immune system for cancer treatment has become a very interesting and

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intense field of study. There have been remarkable improvements in immunotherapy of cancers including monoclonal antibodies, tumor vaccines, therapies targeting immune check points, and T cell therapies based on chimeric antigen receptors [7–9].

During the past decade, our understanding of cellular and molecular networks regulating immune responses in tumor microenvironment has been expanded. Main mechanisms hindering successful immunotherapy include secretion of inhibitory factors, development of tolerant microenvironment by tumors, and antigen switching by generation of escape mutants. According to immunosurveillance hypothesis, the interaction between tumor cells and immune system has 3 phases. In phase 1 the tumor cells are recognized by the innate and adaptive immune systems. During phase 2, tumor cells capable of resisting against immune cells create a dynamic equilibrium; and finally, in the presence of immunosuppressive factors and inadequate co-stimulatory signals they begin to escape from the destruction which is the indication of phase 3 [10].

While novel therapeutic approaches against various cancers have resulted in significant and durable response rates, no reliable treatment have been introduced for complete eradication of the disease. Insufficient immunological responses against tumor cells and their possible mechanisms have thoroughly been investigated, however, the literature is still poor on discussing the complex interrelationships among incompetency of immune cells in defense against tumor cells, metabolic regulation of tumor microenvironment, and the effects of chronic psychological stress in cancer patients. In this review, we will discuss the immune cells involved in the defense against tumor cells; specific cellular cross-talks between immune and tumor cells; and the possible roles of metabolism, chronic psychological stress, and neurotransmitters in tumor microenvironment which render immune cells response relatively ineffective against tumor cells.

2. Insufficiency of immune responses against tumor cells

2.1. Innate immune system; friend or foe

Innate immune response against tumors can be advantageous as it defends against invading pathogens [11]. Anti-tumor response of the adaptive immune system is mediated via the process called “T cell priming” by antigen presenting cells (APCs), particularly dendritic cells (DCs) [5]. Adaptive immune response modulating signaling pathways regulated by the innate immune system have attracted attention to the innate immune receptors and their role in the regulation of tumor microenvironment [5,12]. By contrast, in some cases, chronic inflammation or prolonged immune responses can act as predisposing factors for the cancer development. Moreover, inadequate innate immune response might potentially disrupt tumor recognition by the adaptive immune cells [13].

Pattern recognition receptors (PRRs) are innate immune receptors that recognize endogenous stress signals including damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) [5,14]. Immune response against tumors can be regulated by the activation of PRRs. It has been shown that the stimulation of PRRs by the exogenous ligands can induce antitumor immune responses [15,16]. By contrast, excessive tumor growth has been observed in PRR-deficient animals [17]. Prolonged activation of PRRs under chronic inflammatory conditions may augment tumor progression, and therefore, innate immune system appears to act like a double edged sword in defending against tumors [18,19]. The presence of natural killer (NK), natural killer T (NKT), and Gamma Delta T (γδ T) cells in tumor microenvironment has been documented. Although, these cells might have positive or negative regulatory effects, their net influence is often positive. Moreover, innate immune system directly or indirectly regulates the differentiation of tumor-defending T cells via the cytokines secreted by the activated DCs [5].

NK, NKT, and γδ T cells can be activated in response to inflammation, recognizing various types of ligands expressed by the tumor cells. Therefore, any impaired response by these cells in the tumor microenvironment is associated with the lack of activator signals against tumors [5].

One of the important elements of the innate immune system are plasmacytoid dendritic cells (pDCs) that regulate both adaptive and innate immune responses via secretion of large amounts of interferon type I and other cytokines such as TNF-α, IL-6 and different types of chemokines. In addition, pDCs mediate migration and activation of the innate immune effector cells like monocytes, macrophages, and NK cells, as well as the stimulation of the adaptive immune response. Tumor-associated pDCs are often immature and cannot produce adequate amounts of type I interferon and proinflammatory cytokines. Moreover, the presence of pDCs in the tumor microenvironment has immunosuppressive effects by inducing the Treg cells; therefore, proper activation of pDCs can enhance anti-tumor immune responses [20].

It seems that even if tumor cells were perfectly recognized by innate immune cells population (NK, NKT and γδ T Cells) and also through DAMPs by dendritic cells and macrophages, in the milieu of inadequate stimulatory signals and on the other side in the presence of immunosuppressive signals induction by tumor cells, disability of both innate and adaptive immune systems is not unexpected. On the other hand, if the innate immune responses were not strong enough to stimulate and activate effector cells, merely, recognition and interaction of effector cells with tumor cells won't be efficient [5].

While DAMPs are danger signals capable of stimulating inflammatory processes, they also play a central role in the tissue repair. In fact some DAMPs have been studied for their role in the healing and tissue repair [21]. It is postulated that some type of DAMP recognized by the mast cells, dendritic cells, and macrophages could debilitate immune system in defense against tumor cells by favoring overexpression of suppressive signals with concomitant generation of exhausted effector immune cells. It has been shown that the increased appearance of DAMPs following chemotherapy e.g. after doxorubicin or oxaliplatin favors immunogenic cell death of tumor cells. Destruction of malignant cells following chemotherapy results in the abundance of endoplasmic reticulum chaperones (e.g. calreticulin), ATP, cell-intrinsic type I interferon, high-mobility group box 1, annexin A1, and other DAMPs in the tumor microenvironment, facilitating the activity of APCs especially DCs (Fig. 1) [22].

2.2. Effects of tumor microenvironment on the adaptive immune cells

Direct interaction between APCs and adaptive immune cells such as $CD4^+$ helper T lymphocytes, B lymphocytes, and $CD8^+$ cytotoxic T lymphocytes result in the expression of diverse specific antigen receptors leading to broader, more flexible and augmented immune responses. Adaptive immune responses against tumor cells need initial processing of tumor antigens by APCs especially DCs and T cells priming [23]. DCs as the main specified APCs capture foreign antigens and convey it into lymphoid tissues where they present modified and prepared antigens to adaptive immune cells. In general, DCs stimulate T cells (T $CD8^+$ and T $CD4^+$) and support anti-tumor adaptive immunity, albeit DCs accumulation in tumor micro-environment mostly is impaired [24,25]. Innate lymphoid cells (ILCs), NK cells and other innate immune cells can just detect general patterns like presence and absence of MHC I as well as other exogenous and endogenous ligands and they do not express antigen-specific receptors like T and B lymphocytes [26]. Tumor antigens can be expressed on MHC I and be recognized by adaptive immune cells. Tumor cells can use several mechanisms to down-regulate MHC class I. MHC-deficient tumor cells can escape T cell immune responses which make them more susceptible to NK-cell-mediated lysis [27]. However, it is generally admitted that chronic or imperfect innate immune responses can increase the incidence of cancer development. The role of diverse types of adaptive immune cells in defense against tumor cells is not completely elucidated; but it is well

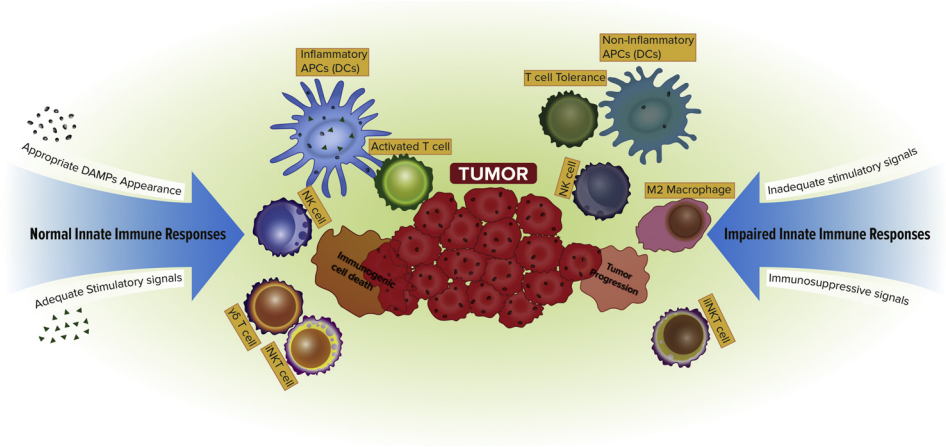

Fig. 1. Immunogenic cell death in tumor microenvironment depends on appropriate DAMPs apperance by tumor cells, DAMPs recognition by innate immune cells (immune response initiator cells) and adequate stimulatory signals as well as proper antigen presentation to adaptive immune cells. In the presence of immunosuppressive mechanisms and/or inadequate stimulatory signals in impaired innate immune responses, effector immune cells might be inactive or functionally impaired in defense against tumor cells.

known that the risk of viral associated cancers is greatly higher in immunocompromised individuals [28]. T cells are involved in various immune responses including infection, allergy, cancer, and autoimmune diseases. $CD8^+$ T cells (CTLs) and $CD4^+$ T helper type 1 (Th_1) are the principle weapons of adaptive immune defense against the intracellular bacteria and viruses as well as the cancers [29,30]. In fact, over centuries of evolution, type 1 adaptive immune response has been shaped against acute infections rather than cancers. Prolonged type 1 immune response can lead to continuous tissue damage and for this reason shortly after the initiation of this type of response, a range of inhibitory mechanisms are arranged by normal immune system to prevent self-damages [31]. Debilitation of T cell activity by any reason negatively affects anti-tumor defense. Therefore, in the circumstances of prolonged immune responses, it is not surprising that both CTLs and T helper 1 cells mostly fail in defense against tumors [32]. As discussed previously, APCs in tumor microenvironment are tolerogenic with low level expression of co-stimulatory ligands such as B7.1 (CD80) and B7.2 (CD86) leading to impaired activation of anti-tumor T cells [33,34].

2.3. Direct T cell inhibition in tumor microenvironment

Multiple factors are able to inhibit anti-tumor T cell activity in the tumor milieu; some affected by the acquired derangements like genetic alterations in the immune cells. Examples of this phenomenon are: 1) Promoted activity of Wnt/β-catenin signaling pathway in melanoma cells which suppresses the recruitment of APCs and T cells priming [35]; 2) Decreased production of Th_1 chemokines i.e. CXCL9 & CXCL10 due to epigenetic silencing during immune response against ovarian cancer cells [36]; and 3) overexpression of programmed death-ligand 1 (PD1L) by tumor cells [37,38]. By contrast, others are the sequel of evolutionarily conserved inhibitory mechanisms of T cells [39], that are not tumor-specific and can be activated in any tissue; these mechanisms are aimed at preventing lymphocyte toxicity following prolonged infection or inflammation; otherwise, immune responses cause unwanted damages to host tissues and organs. It should be underlined that this natural phenomenon plays a negative role in immune defense against tumor cells [5,40].

In recent years, cytotoxic T lymphocyte antigen 4 (CTLA-4) and PD1 have been determined as remarkable factors leading to T cells exhaustion and anergy in tumor microenvironment [32]. Immune checkpoint blockade by CTLA-4 and PD-1/PD-L1 antagonists is an important strategy aimed at reversing immunosuppressive theme in the tumor microenvironment. It has been shown that anti-CTLA-4 and anti-PD-1/PD-L1 based immunotherapies are able to restore immune responses against tumor cells [41]. However, some reports mention that monotherapy with these agents are not fully effective and new strategies implementing multiple therapy are at the focus of research [42].

Regulatory T cells possessing immunosuppressive effects exist in large quantities in the tumor microenvironment. Tumor immunosurveillance is carried out by the effector T cells and NK cells and could be suppressed by the Treg cells [43]. Accumulation of Regulatory T cells and Myeloid suppressor cells have been found in the neoplastic tissues [44,45], resulting in the failure of anti-tumor immune response of effector T cells by releasing immunosuppressive cytokines such as transforming growth factor beta (TGF-β), interleukin 10 (IL-10). Moreover, up-regulation of CTLA4 by the Treg cells which is a CD28 cognate and antagonizes the effects of co-stimulatory ligands like B7.1 & B7.2 has been noted. Intra-tumoral expression of chemokines such as chemokine (C-C motif) ligand 17 (CCL17), CCL22 and CCL28 can facilitate the recruitment of Tregs. While it is not known clearly that how tumor microenvironment supports the presence and excessive activity of Treg cells, metabolic regulation of immune cells by the tumor microenvironment may help the activity and survival of these cells (Fig. 2A) [32].

3. Metabolic regulation of immune cells by tumor microenvironment

In the process of T cells stimulation to gain effector function, various alterations in the metabolic pathways occur that affect T cells functionality. Furthermore, tumor cells have distinct metabolic pathways and secrete various metabolites in the tumor microenvironment which may inhibit T cells activity [46].

For the first time in 1920, Otto Warburg showed that cancer cells produce energy from glycolysis even under normal oxygen concentrations which is known as “Warburg effect”. As a result, ATP production in tumor cells is mainly dependent on the conversion of glucose to lactate through aerobic glycolysis rather than mitochondrial oxidative phosphorylation [47]. Although, ATP production through glycolysis is very fast, it is not efficient due to the lower number of ATPs produced per unit of glucose. Therefore, tumor cells consume a higher amount of glucose in comparison with normal cells to meet their metabolic requirements. The sustained aerobic glycolysis in tumor cells is due to alterations in oncogenes or tumor suppressor genes. Glucose is composed of carbon, oxygen, and hydrogen and cannot provide all building blocks for rapidly dividing tumor cells. Therefore, to proliferate and build new cells they need nutrients other than glucose [48]. Furthermore, cancer cells produce higher amounts of H^+ (lactic acid and carbonic acid, which are end-products of metabolic pathways) in comparison to normal cells as a result of higher metabolic rates [49]. Therefore, it can be hypothesized that all these alterations in tumor microenvironment lead to deficient essential nutrients and enhanced metabolic end-products which has destructive effects on the surrounding normal and immune cells.

On the other hand, the metabolic profile of T cells is regulated depending on their differentiation state. The primary metabolic needs of

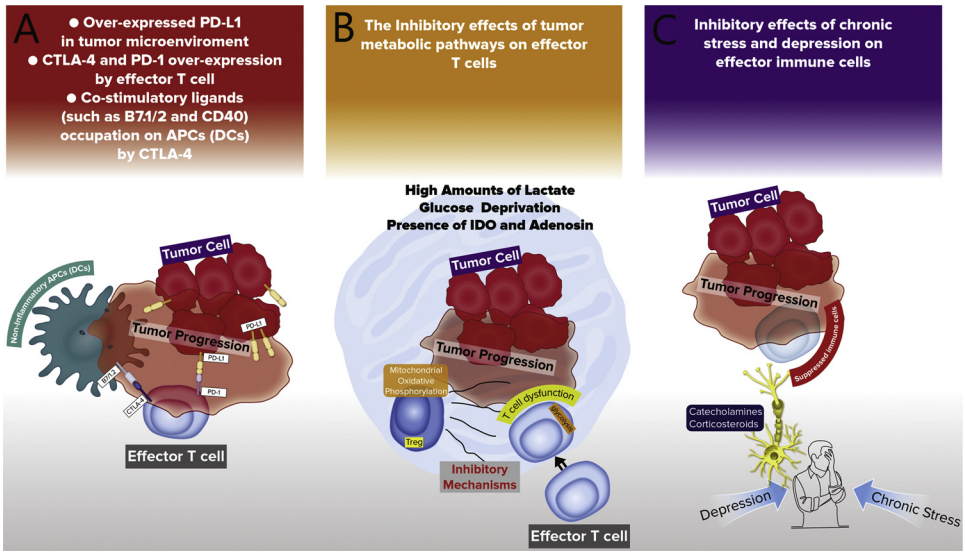

Fig. 2. Three main disabling parameters in immune defense against tumor cells. A) Direct interaction between immune and tumor cells: over-expressed PD-1L by tumor cells, CTLA-4 and PD-1 over-expression by effector T cells and co-stimulatory ligands occupation on APCs by CTLA-4 can have remarkable roles in immune response failure against tumor cells. B) metabolic regulation of immune cells by tumor microenvironment. Activated T cells switch their metabolism to glycolysis. Lactate as the main product of glycolysis can down-regulate energy consumption by effector T cells interfering with their normal activities. In the opposite tumor metabolism cannot affect Treg cells (mitochondrial oxidative phosphorylation) and Treg cells can be quite functional in tumor microenvironment. Also glucose deprivation, indoleamine 2,3 oxygenase (IDO) and adenosin presence can impair the function and activity of effector T cells. C) chronic stress and depression in patients challenging with high morbid diseases like cancer can have inhibitory effects on immune responses against tumor cells. Chatecholamines and corticosteroids elevation in cancer patients may have negative influences on immune responses against tumors.

resting naïve T cells are mainly dependent on the mitochondrial oxidation of pyruvate or fatty acids to provide the basal ATP requirements. Upon T cells stimulation after encounter with antigen, they alter their metabolic and signaling pathways toward proliferation and immune functionality. This includes metabolic shift mainly focused on production of biosynthetic intermediates such as proteins, nucleic acids, and membrane components which are essential for cell growth and proliferation [50]. To provide the metabolic and biosynthetic needs for effector function, they enhance glucose uptake and glycolysis. It has been reported that activated T cells exhibit higher rates of glycolysis, amino acid metabolism, and fatty acid synthesis as seen in most tumor cells. After the termination of immunogenic response, memory cells remain in the circulation in order to respond immediately upon facing the same antigens. Memory cells have been shown to be mainly dependent on the mitochondrial oxidative phosphorylation, similar to naïve T cells. Treg cells show the same metabolic profile as in naïve cells; however, Th1 and Th17 cells depend mostly on glycolysis [51].

Signaling pathways inside the cells can determine metabolic fate in T cells. The mammalian target of rapamycin (mTOR) is a member of phosphatidylinositol 3-kinase (PI3K) family of kinases which is involved in various cellular processes. mTOR is the core component of mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) [52]. Activation of mTORC1 by PI3K determines the type of T cells subsets. mTORC1 can also be activated by mechanisms other than PI3K such as the availability of essential nutrients. Activation of mTORC1 is essential for generation of effector T cells in which up-regulates glycolysis and pentose phosphate pathway. However, cells lacking mTORC1 mostly generate Treg cells [53,54]. Inversely, AMP-activated protein kinase (AMPK) negatively regulates mTORC1 and inhibits glycolysis pathway, while, enhances ATP production by mitochondrial oxidative phosphorylation. Therefore, activation of AMPK leads to production of Tregs [55].

The metabolic similarity between activated T cells and tumor cells in tumor microenvironment leads to a competition between these cells for glucose, amino acids, and other nutrients uptake. The higher glycolytic rate and nutrients uptake as well as poor vascularization around most solid tumors, lead to nutrients deprivation in tumor microenvironment which restricts effector T cells function. It has been shown that tumor cells with high rate of glycolysis can deplete glucose in tumor microenvironment which leads to exhausted T cells with a low anti-tumor ability and cytokine production [56]. There is also growing evidence about the importance of amino acids to preserve T cells effector functionality, biosynthesis, and proliferation. Therefore, higher amino acids uptake by most tumor cells leads to suppressed T cells anti-tumor activity [57]. Recently, Geiger and colleagues carried out a study to investigate the proteome and metabolome profile of naïve T cells after activation. They found that intracellular arginine content is crucial for T cells functionality and anti-tumor responses [58]. In another study, Ravishankar and coworkers showed that tryptophan deficiency is immunosuppressive [59]. Due to the high rate of fatty acids uptake by either T cells or tumor cells, fatty acids are other nutrients that these cells compete for in tumor microenvironment [60]. High metabolic needs of effector T cells and nutrient deprivation in tumor microenvironment, lead to survival of Tregs as they are able to produce energy from sources other than glucose. This may further restrict the function of effector T cells in tumor site.

In addition to key nutrients deprivation in tumor microenvironment, tumor cells generate and secrete some end-products that are toxic for T cells and inhibit their action. The most important waste product by tumor cells is lactate which is accumulated due to high rate of glycolysis. It has been shown that extracellular lactate accumulation reduces the proliferation and cytokine production of cytotoxic T cells by 95%. The cytotoxic activity of T cells was also suppressed by lactate up to 50%. Furthermore, effector T cells produce and secrete lactate due to their glycolytic metabolism. This is especially important because intracellular lactate accumulation is harmful for T cells and they rely on lactate secretion. Since, lactate secretion by T cells depends on the concentration gradient between cytoplasmic and extracellular lactate, higher extracellular lactate concentration due to tumor cells metabolism blocks lactate secretion by T cells [61]. In addition to that, lactate has been shown to impair $CD4^+$ and $CD8^+$ T cells motility via interference with chemokine receptors [62].

Indoleamine 2, 3-dioxygenase (IDO) is an enzyme which is involved in the tryptophan metabolism and converts tryptophan to kynurenine. This enzyme is overexpressed in most tumor cells and is associated with poor tumor prognosis and avoidance of immune attack [63]. In addition to immunosuppressive effects of kynurenine, reduced amounts of tryptophan caused by IDO impairs effector T cells metabolism in tumor site [59]. Tryptophan depletion can be also occurred by the activity of Tregs as they are able to promote the expression of IDO in dendritic cells [64]. Further to Tregs, other type of cells also exist in tumor microenvironment such as myeloid-derived suppressor cells (MDSCs) which are able to reduce arginine and tryptophan levels, leading to suppressed anti-tumor responses [65,66]. Adenosine is another waste

Table 1
A summary of limiting resources and waste products caused by tumor cells in tumor microenvironment which affects effector T cells function.

Limiting Resources in Tumor Microenvironment	Ref	Toxic Waste Products Produced by Tumor Cells in Tumor Microenvironment	Ref
High glucose uptake by tumor cells due to high glycolysis rate	[56]	Lactate production due to high glycolysis rate	[61]
High amino acid uptake by tumor cells	[57]	Kynurenine production due to Indoleamine 2, 3-dioxygenase deficiency	[59]
Fatty acids uptake by tumor cells	[60]	Adenosine excess due to ATP hydrolysis	[67]
Poor vascularization around most solid tumors	[56]		
Arginine deficiency due to arginase overexpression	[58]		
Tryptophan deficiency due to Indoleamine 2, 3-dioxygenase overexoression	[59]		

product generated by tumor cells which has immunomodulatory effects. Adenosine is generated in the process of extracellular ATP hydrolysis. The immunosuppressive effects of adenosine is mediated by adenosine receptor (A2R) [67]. Tregs have also shown to express CD39 which allows them to hydrolyze extracellular ATP [68]. This is another mechanism contributing to immunosuppressive effects of Tregs in tumor microenvironment. Table 1 summarizes the key nutrients uptake and waste products in tumor microenvironment which restricts effector T cells function.

Taken together, understanding the metabolic similarities and differences between tumor cells and different types of T cells is important to improve the efficacy of anti-tumor immune responses. Several approaches have been taken on this goal with some improvements, but metabolic similarities between tumor cells and effector T cells make it difficult to achieve. Therefore, investigations to find better strategies are still needed for successful immunotherapy responses (Fig. 2B).

4. Impact of chronic psychological stress on tumor immunosurveillance

Cancer patients have low quality of life due to high rate of morbidity and mortality and disabling influences of cancer. They mostly suffer from elevated stress, depression, and bad mood which have inhibitory effects on the immune responses against tumor cells. Chronic activation of hypothalamus-pituitary-adrenal axis due to persistent stress and depression can impair immune responses resulting in the development and progression of tumors. In general, stress and depression have undeniable impacts on reduction of CTLs and NK cell activities affecting the process of tumor immunosurveillance [69]. In addition to improving life quality, treatment of depression increases survival rates in cancer patients. Duration of stress is an important factor affecting suppression of immune responses. Short-term stress can accelerate immune activation and exacerbate innate and adaptive immune responses; while, on the other side, chronic stress has been reported to be immunosuppressive [70,71].

A long-standing hypothesis states that psychosocial stress can influence the incidence and progression of tumors. The bidirectional communication between psychological states and immune system dates back to 200 years B.C when Galen suggested that melancholic women carry a higher risk of developing breast swelling. In 1936, Hans Selye defined stress as a potent activator of sympatho-adreno-medullary system and hypothalamic-pituitary-adrenal axis activator [72,73]. In response to stress, circulating levels of various hormones including glucocorticoids and catecholamines can be increased, mobilizing energy sources to adapt the individual to the new conditions [74]. Communications among CNS and immune system can be mediated through chemical messengers, endocrine organs, and immune cells receptors affecting both networks in a bidirectional pathway. Neurotransmitters such as dopamine, norepinephrine, acetylcholine, and serotonin; neuropeptides like substance P, enkephalins, and neuropeptide γ, as well as neurohormones such as adrenocorticotropin hormone, prolactin, and adrenal hormones (epinephrine and corticosteroids) can affect immune system function according to *in vitro* and *in vivo* studies and there is evidence indicating that lymphocytes and macrophages have direct receptors for the mentioned molecules and factors [75–77].

Stress-related catecholamines are suggested as immunosuppressive factors. Studies have indicated that high concentrations of corticosteroids during stress have important inhibitory effects on lymphocyte and macrophages function as well as inflammatory cytokines and mediators [69].

Glucocorticoids, crucial lipid hormones, are involved in immune system regulation [78]. Glucocorticoid-induced TNF family-related receptor (GITR) stimulation can induce a variety of T cell responses ranging from apoptosis to proliferation [79]. Generally, GITR cross-linking with agonistic antibodies can shift effector responses of the conventional $CD4^+$ and $CD8^+$ T cells both into chronic viral infections or tumor cell expansion [80]. In general, glucocorticoids have been documented as anti-inflammatory and immunosuppressive factors. Several studies have reported that increased glucocorticoid receptors activity can contribute to tumor cell survival [81–83].

Dopamine is a catecholamine, plasma levels of which are greatly increased in cancer patients [84]. It has been reported that dopamine together with catecholamines can affects lymphoid organs and immune cells function through sympathoadernergic terminals [85]. Stimulation of type I DARs expressed on human naive $CD4^+$ T-cells potentiates the production of Th2 cytokines [84]. Furthermore, type I DARs stimulation on human Treg cells can inhibit secretion of TGF-β and IL-10 [86]. Additionally, stimulation of D2R and D3R in normal human resting T-cells encourages the secretion of IL-10 and TNF-α [87].

Anti-tumor immune response can be suppressed in cold stressed mice due to increased levels of norepinephrine [88]. When mice were housed at the thermo-neutral temperature, circulating levels of norepinephrine were significantly reduced and mice developed superior control of tumor growth [89]. It has been recognized that immunosuppression mediated by release of norepinephrine could be reversed by pan-β-adrenergic antagonist such as propranolol. Additionally, adrenergic blockade results in enhanced tumor control and can increase the efficacy of the immune checkpoint inhibitors such as anti-PD-1 [90]. Improved anti-cancer effects of β-adrenergic inhibition are dependent on $CD8^+$ T-cells [91]. Since the β2-adrenergic receptors are the primary subtypes expressed on immune cells [91], it has been documented that the immunosuppressive effects of norepinephrine can be mediated via the β2-adrenergic receptors [90]. Indeed, it has been identified that activated and memory CTLs express β2-adrenetgic receptors, and their functions are disturbed by β2-adrenergic signaling [92]. Besides, it has recently been demonstrated that β2-adrenergic stimulation can suppress metabolic reprogramming and might, accordingly, be a major mechanism by which adrenergic stress represses anti-tumor cellular immune responses [93].

In fact, since cancer is a chronic disease and immune responses are already compromised as we discussed in several perspectives in this study, the parameters such as stress, frustration and depression in patients might have powerful negative influences on immune responses against tumor cells and it could be regarded as an obstacle for successful immunotherapy of cancer (Fig. 2C).

5. Conclusion

Cancer immunotherapy has brought a new era to survival and a hope to treatment of tumors. Despite progress in cancer

immunotherapy *in vitro*, most *in vivo* investigations remain as just promising therapies to be developed more in the future. Insufficiency, lack of stimulatory signals, as well as multiplicity of immunosuppressive mechanisms in the tumor microenvironment are main factors hindering successful immunotherapy. Moreover, production of metabolites like lactate by tumor cells has inhibitory effects on the effector immune cells which affects tumor immunosurveillance. Additionally, negative impact of psychological factors such as chronic stress and depression on the immune system hamper successful cancer immunotherapy. Therefore, obviating inhibitory effects of metabolic and psychological factors in cancer patients, could potentially improve the outcome of cancer immunotherapy. We believe that simultaneous control of metabolic and psychological negative influences on the tumor immunosurveillance, along with addressing the weak aspects of innate and adaptive immune responses in cancer immunotherapy may result in more successful treatment of tumors. This study presents a new perspective on factors affecting immune responses against tumor cells with the possibility of interference with immunotherapy of cancers. Although, we have shown the possible association of mentioned factors with unsuccessful immunotherapy, this field of study needs further investigations especially on the individual differences of metabolism status and psychological states.

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