

Interplay between Immune Checkpoint Proteins and Cellular Metabolism

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Abstract

With the recent successes in immuno-oncology, renewed interest in the role of immune checkpoint modulators, such as the B7 family proteins, has escalated. The immune checkpoint proteins play a crucial role in the regulation of cellular immunity; however, their contribution to other aspects of cancer biology remains unclear. Accumulating evidence indicate that immune checkpoint proteins can regulate metabolic energetics of the tumor, the tumor microenvironment, and the tumor-specific immune response, leading to metabolic reprogramming of both malignant cells and immune cells involved in mounting and sustaining this response. Immune cell metabolism impacts the activation status of immune cells and ultimately the immune

response in cancer. Tumor cells may deplete nutrients that immune cells require for optimal generation, expansion, and function. They may also generate toxic metabolites in the microenvironment or induce conserved inhibitory pathways that impair immune function and thus inhibit antitumor responses. In this review, we will discuss how cancer cells with altered expression of immune checkpoint proteins can potentially inhibit immune function through the alteration of cellular and microenvironmental metabolism, providing a new perspective on the interplay between these pathways and offering a potential therapeutic intervention strategy in the treatment of malignant disease. *Cancer Res*; 77(6); 1245–9. ©2017 AACR.

Introduction

Cancer cells differ from normal cells in the metabolic machinery used to support cell proliferation and survival. This dysregulated metabolism has been regarded a hallmark of cancer. Energy production in most cancer cells shows a distinct feature that is dependent more on aerobic glycolysis (also known as Warburg effect) instead of mitochondrial oxidative phosphorylation (OXPHOS; ref. 1). Although glycolysis is a physiologic response to hypoxia in normal tissues, cancer cells constitutively take up glucose and produce lactate regardless of oxygen availability (2). This increase in glycolytic flux allows rapid production of ATP and intermediates of the glycolytic pathways to fulfill the metabolic demands of proliferating cells. Cancer cells also show an increase in biosynthetic pathways leading to the

production of macromolecules required for growth and proliferation (3). Reactive oxygen species (ROS) are a diverse class of radical species that can have different roles depending on their concentration. In cancer cells, the same oncogenic mutations that promote altered metabolism and oncogenic signaling also result in high rate of ROS production (4). Although the precise molecular mechanisms underlying dysregulated cellular metabolism in cancer cells are not completely understood, emerging evidence shows that this altered metabolism contributes to enhanced cancer cell proliferation, survival, drug resistance, and invasion/metastasis.

The immune system plays a crucial role in the protection of the animal or human against pathogens and cancers. It is typically divided into two categories: innate immunity and adaptive immunity. Adaptive immunity refers to a complex, antigen-specific immune response. Once an antigen is processed and then recognized, the adaptive immune system produces a plethora of immune cells specifically attacking that particular antigen, and creates a "memory" that makes future responses to that antigen more efficient. When the immune system mounts a cell-mediated response to foreign antigens, the adaptive immunity recruits a variety of effectors including CD8⁺ cytotoxic T cells and CD4⁺ helper T cells (5). Three signals are required for T-cell activation (5, 6). First, T-cell receptors must engage specific peptides presented by MHCs on antigen-presenting cells (APC) or the cancer cell. Second, specific receptors on T cells must bind ligands expressed on APCs or cancer cells to prevent anergy, which refers to failure to mount the response against an antigen. Third, signals provided by cytokines play a critical role in regulating the strength and type of immune responses. There are multiple costimulatory or coinhibitory interactions among APCs and T cells (Fig. 1A; Supplementary Table S1; ref. 6), providing a key checkpoint in the regulation of T-cell immunity

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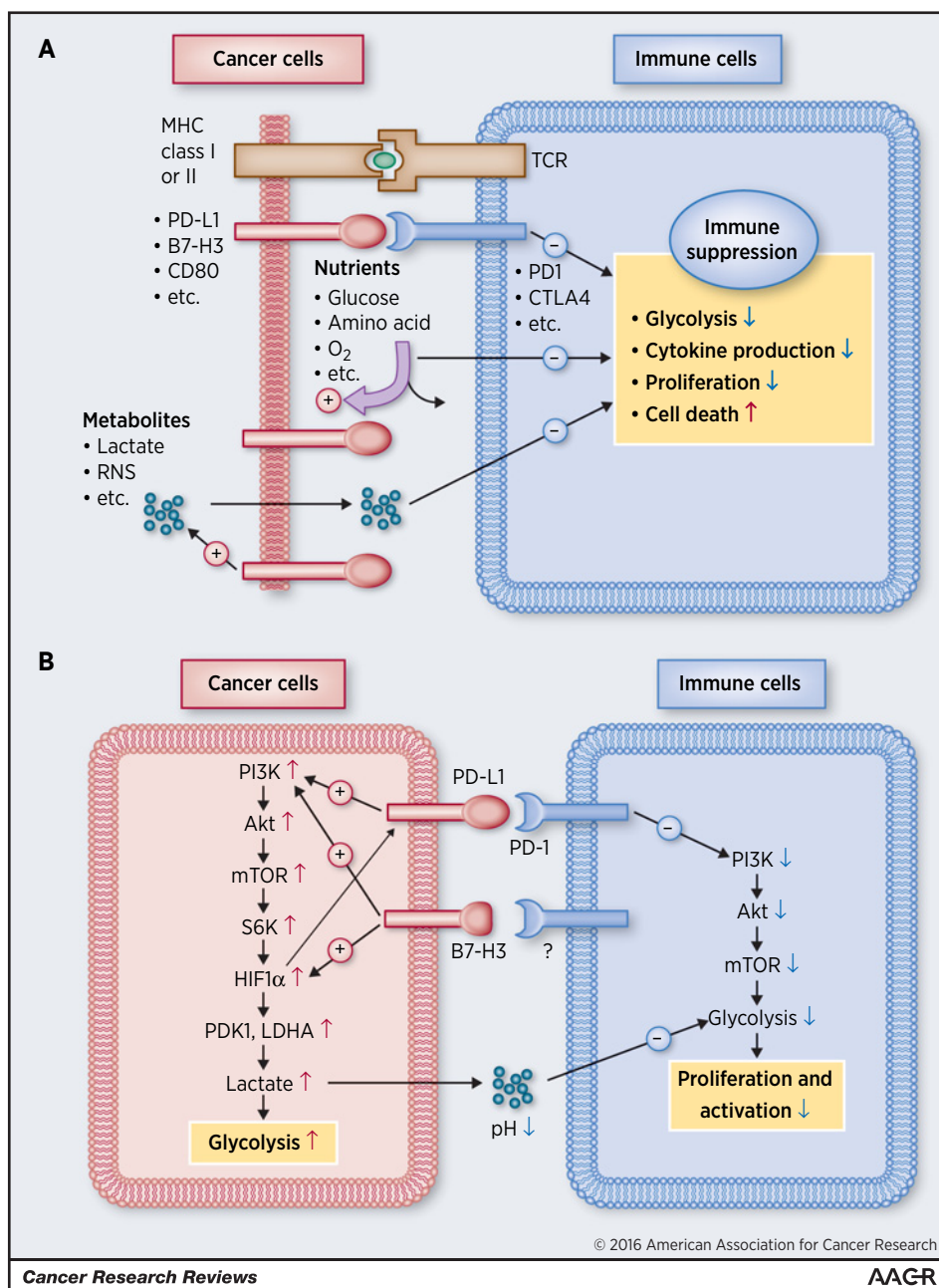
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**Figure 1.**

The interplay between immune checkpoint proteins and cellular metabolism. **A**, Immune checkpoint proteins can affect cellular metabolism and immune cell activation by (i) receptor/ligand ligation on cancer cells and immune cells, (ii) nutrients' competition, and (iii) cancer cell-produced metabolites. **B**, Impact of immune checkpoint proteins on glycolytic signaling pathway. These signaling processes can suppress the immune cells, leading to escaping immune surveillance, and consequently promote cancer progression.

and maintenance of immune homeostasis. These costimulatory or coinhibitory proteins either can turn up a signal (costimulatory) or turn down a signal (coinhibitory) in the immune system and are referred to as immune checkpoint proteins.

Immune cells, such as lymphocytes, also use Warburg effect like glycolytic pathways to accommodate their bioenergetics needs. Quiescent naïve T cells rely on OXPHOS and use glucose, amino acids, and fatty acids for basal cellular needs. During the process of activation, these cells reprogram themselves to glycolytic metabolism to adapt to the increased energy requirements (7, 8). Intriguingly, several recent studies have shown that the aberrant expression of immune checkpoint proteins is associated with tumor cell metabolic changes. The crosstalk between these

immune checkpoint proteins and cellular metabolism may have a profound impact on cancer cell evasion from the immune system.

Immune Checkpoint Proteins

Immune checkpoint proteins regulate the immune response to maintain self-tolerance and prevent excessive inflammatory reactions. Many different ligands/receptors are involved in the coordinated actions of an effective and efficient immune response (Supplementary Table S1). Several unique classes of checkpoint proteins exist, and among these are the TNFR superfamily (9) and B7 family (10), which can influence immune cells differently

based on their expression patterns. Cancer cells can disrupt the immune response through the overexpression of inhibitory molecules like PD-L1 (Fig. 1A; ref. 11) or the loss of expression of stimulatory molecules like CD40L (12). Tumors can evade immune surveillance even in the presence of tumor antigens because the immune cells may not receive adequate signals for activation and proliferation or are suppressed by inhibitory checkpoint proteins (13).

Suppressing immune-inhibitory checkpoint proteins can enhance immune responses, prevent cancer progression, and improve patient survival (14). The goal of effective immunotherapy is to activate the patient's own immune system to eliminate cancer with high selectivity, low toxicity, and durable responses that can recognize neoantigens arising in evolving tumors (15). Several immune checkpoint proteins were shown to be dysregulated in tumors and immune cells and contribute to immune evasion. Blockade of these inhibitory checkpoint proteins has been intensely pursued in recent years as a strategy to enhance T-cell infiltration and effector functions in cancer. Blocking antibodies against the T-cell coinhibitory receptors or ligands, such as CTLA-4, PD-1, and PD-L1, have shown promising efficacy in advanced melanoma, non-small cell lung carcinoma, renal cell carcinoma, bladder cancer, and lymphoma (16–18).

Metabolic Interplay between Tumor and Immune Cells

Along with direct interaction between tumor and immune cells, an indirect mechanism of immune response modulation has been investigated. Several recent studies reported that the metabolic interplay between tumor and immune cells in the tumor microenvironment plays an important role in the immune response regulation (19, 20). Nutrient competition is one such metabolic mechanism involved in tumor immune evasion (Fig. 1A). In growing tumors, deprivation of environmental nutrients, such as glucose or amino acids, by rapid proliferation, high rates of glycolysis or overexpression of tumor-specific molecules can inhibit T-cell functions (21). Activation of T cells and their effector functions relies on the activation of distinct signaling pathways leading to metabolic reprogramming. Metabolic reprogramming in T cells increases energy demand and is crucial for the triggering of effector T-cell activation. A decreased level of nutrients within the tumor microenvironment can lead to T-cell "anergy" or dormancy to spare energy or to preferentially activate autophagy as a survival mechanism to counteract nutrient insufficiency (22). Chang and colleagues described a competition between tumor cells and tumor-infiltrating T lymphocytes (TIL) for glucose within the tumor niche that can drive cancer progression through metabolic competition (20). In this study, tumor PD-L1 expression promoted glycolysis and Akt/mTOR activation in tumor cells while suppressing mTOR activity in T cells through glucose competition. Checkpoint blockade with anti-PD-L1 antibodies inhibited tumor progression and glucose uptake in tumor cells and increased mTOR activity and glucose uptake of T cells (Fig. 1B). Remarkably, two other checkpoint blockade antibodies, anti-PD-1 and anti-CTLA-4, were also shown to cause changes in extracellular glucose concentrations, although the mechanisms underlying these metabolic changes are still not fully understood (20). Akt/mTOR activation is known to promote glycolysis via enhanced HIF-1 α activity, which addition-

ally sustains fatty acid and protein synthesis to support malignant cell survival. Rao and colleagues found that in solid tumors mTOR activation of TILs tuned a balance between effector and memory CD8⁺ T cells by regulating expression of a T-cell-associated transcription factor, T-bet (23). They also showed that the immune checkpoint molecule B7-1 induced mTOR kinase activity in naïve CD8⁺ T cells via PI3K and STAT4 pathways. Blocking mTOR activity by rapamycin reversed IL12-induced effector functions consistent with T-bet loss. Consequently, mTOR signaling has an important role in metabolic reprogramming and nutrient competition in both tumors and immune cells, and immune checkpoints including PD-L1 and B7-1 can mediate metabolic reprogramming through mTOR signal pathway. Furthermore, PD-1 intrinsically expressed in melanoma cells, but not lymphocytes, has also been shown to upregulate Akt/mTOR signaling in cancer cells, with the phosphorylation status of two intracellular motifs of PD-1, ITIM, and ITSM, being critical for this modulatory role (24).

Recently, B7-H3 has been reported to regulate cancer cell metabolism (Fig. 1B). Lim and colleagues reported that the expression of B7-H3 metabolically reprograms cancer cells by increasing HIF-1 α activity, glucose uptake, and lactate production in breast cancer cells (25). They showed that B7-H3 enhanced glycolysis in tumor cells through upregulating HIF-1 α and its target proteins, LDHA and PDK1, whereas knocking down B7-H3 suppressed glycolysis and tumor growth *in vitro* and in a breast cancer xenograft mouse model. Nunes-Xavier and colleagues also showed that B7-H3 activated the Akt/mTOR pathway and increased glycolytic capacity in breast cancer cells (26) and observed that B7-H3 confers resistance to mTOR inhibitors. These reports raise the possibility that tumor cell-expressed immune checkpoint proteins, such as B7-H3, can promote glycolysis in tumor cells and cause nutrient competition between tumor cells and immune cells in the tumor microenvironment.

In addition to nutrients' competition, accumulation of toxic metabolites in the tumor microenvironment can also impact the interplay between tumor cells and immune cells (Fig. 1A). The byproduct of aerobic glycolysis, lactate, is secreted from the tumor cells and accumulates in the microenvironment, resulting in local acidification known as acidosis. Acidosis in the tumor microenvironment can suppress proliferation and cytokine production in cytotoxic T cells (CTL) and limit CTL antitumor activity (27). The tumor microenvironment is characterized by a consistent reduction in oxygen resulting in hypoxia-induced upregulation of HIF-1 α and the expression of PD-L1 in tumors, leading to inhibition of T-cell-mediated cytotoxicity and immune escape (28). Taken together, experimental evidence indicates that acidosis induced by hypoxia and HIF- α activation can result in the upregulation of immune checkpoint proteins such as PD-L1 that further contribute to the inhibition of T-cell antitumor responses.

Similar to glucose metabolism, amino acid metabolism can play a regulatory role in T-cell activation. For example, tumor indoleamine 2, 3-dioxygenase (IDO), an enzyme that converts tryptophan to kynurenine and generates NAD, has been shown to deplete the essential amino acid, tryptophan, in the microenvironment, resulting in T-cell inhibition (21). Another amino acid, arginine, is tightly regulated by two enzymes, nitric oxide synthase (NOS) and arginase (ARG). While ARG hydrolyzes arginine to ornithine and urea, NOS oxidizes arginine to

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citruilline and nitric oxide (NO). Several reports have documented that the inducible isoform of NOS (iNOS) is highly expressed and ARG activity is upregulated in diverse cancer types and can be regulated by acidosis (29). A large amount of NO generated by both enzymes is capable of either promoting or inhibiting tumor progression and metastasis depending on the concentration, duration of exposure, and cellular sensitivity to NO (30). Peroxynitrite is one of the reactive nitrogen species (RNS) produced by the reaction between NO and reactive oxygen species within the tumor, and has been shown to induce apoptosis in T cells (31). As a consequence of high RNS production, the tumor microenvironment may become unsuitable for T-cell activation, expansion, and effector function. Indeed, numerous reports indicate that peroxynitrite negatively affects T-cell immunity. The connection between immune checkpoint protein regulation and amino acid metabolism has not been well elucidated, but deserves further study.

Lipid metabolism has also been implicated in immune response regulation. Recently, Yang and colleagues showed that cholesterol metabolism can modulate CD8⁺ T-cell antitumor activity (32). Acetyl-CoA acetyltransferase 1 (ACAT1) is a cholesterol esterification enzyme that converts free cholesterol to cholesteryl esters for storage. The inhibition of ACAT1 led to enhanced effector function and proliferation of CD8⁺ T cells due to increase in plasma membrane cholesterol levels. ACAT1-deficient CD8⁺ T cells showed a reduction of tumor progression and metastasis *in vivo*. A combination treatment of ACAT1 inhibitor and anti-PD-1 antibody improved antitumor efficacy. Importantly, recent work by Patsoukis and colleagues (33) showed that PD-1 prevents effector T-cell development by inhibiting glycolytic reprogramming and promoting fatty acid oxidation (FAO) of the activated CD4⁺ T cells' endogenous lipids through overexpression of carnitine palmitoyltransferase I (CPT1A), a rate-limiting step enzyme in the mitochondria responsible for the β -oxidation of long-chain fatty acids. Their data also revealed that increased FAO was accompanied by upregulation of the major triacylglycerol hydrolase ATGL.

Intriguingly, Le and colleagues found that patients with mismatch repair defects showed a clinical benefit of immune checkpoint blockade with pembrolizumab (34). When treated with the PD-1 antibody, patients with mismatch repair-deficient cancers showed a 40%–71% objective response rate while mismatch repair-proficient patients were unresponsive to the same treatment regimen. In addition, patients with a mismatch repair deficiency showed longer progression-free survival intervals. As DNA damage response has been shown to regulate metabolic homeostasis (35), we speculate that there is a possibility that a deficiency in DNA damage repair may cause dysregulation of cellular metabolism including oxidative stress, mutations in metabolic genes, and activation of metabolic signaling pathways, to create a favorable microenvironment benefitting immune checkpoint manipulation of the antitumor immune response.

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Concluding Remarks and Future Directions

In summary, we have discussed how cancer cells with dysregulated expression of immune checkpoint proteins inhibit immune cells by altering cellular and microenvironmental metabolism. Several lines of evidence suggest that the metabolic interplay between tumor and immune cells plays an important role in immune response regulation. The evidence raises a strong argument that therapeutic limitations may exist in the absence of a combinational strategy to address both aspects (36). For example, immune cells can be activated by targeting an overexpressed inhibitory checkpoint protein present on cancer cells, but the immune cells may not be able to sustain their energetic needs without a metabolically favorable environment. Currently, multiple antibodies have been developed against immune checkpoint proteins (37), and a few promising metabolic targets in cancer have been identified (38). A combinational strategy such as drug-antibody conjugates (39) or nanoparticles (40) could be specifically designed to target a checkpoint protein overexpressed in cancer cells like B7-H3 (41), which would inhibit immune suppression, and to target delivery of a metabolic drug into the tumor cells. Future studies should address the mechanistic connection between immune checkpoint proteins and the metabolism of cancer and immune cells, which may not be independent variables as we once thought. Unanswered and important questions remain including: What is the underlying mechanism of metabolic reprogramming in cancer cells and immune cells by immune checkpoint proteins? Is there a therapeutic window to exploit metabolic interventions in immuno-oncology? How can the metabolic contributions mediated through checkpoint proteins be targeted to maximize antitumor effects? Do specific nutrients or metabolites affect the immune responses more than others (activation, energy, death)? How do metabolic changes in normal tissues and the tumor niche impact the development and maintenance of a favorable immune response? Does metabolic function of the tumor or immune cells contribute to the outcome of immune checkpoint therapy? Answering these questions will expand our understanding of the interplay between metabolic regulation and the immune response, potentially providing new avenues to improve cancer immunotherapy.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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