Metabolic Impact of Immune-Suppressor Cells in Cancer Patients

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Abstract

Immune checkpoint inhibitors (ICIs) are not equally effective for all patients, regardless type of cancer. Immune-suppressor cells, including regulatory T (Treg) cells, tumor associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs), and their metabolic pathways in the tumor

microenvironment (TME) play important roles in resistance to ICIs. Although Treg cells, TAMs and MDSCs play significant roles in immunosuppression in the TME, these cells are very important in the orchestration of metabolism such as angiogenesis and production of indoleamine 2,3-dioxygenase (IDO) and nitric oxide (NO) towards tumor escape, progression and expansion. Cancer immunotherapies tailored with metabolic characterizations such as parameters of angiogenesis, inflammation or obesity may be needed for the establishment of a successful treatment modality in the immunotherapy era.

Keywords: Tumor associated macrophages (TAMs); Regulatory T (Treg) cells; Myeloid-derived suppressor cells (MDSCs); Cancer immunotherapy; immunosuppression

Introduction

Immune checkpoint inhibitors (ICIs) have been developed, and now leading to a change in the entire therapeutic algorithm in many malignant diseases. However, ICIs are not equally effective in all cancer patients, and their response rates have been reported to be different among patients [1-4]. Moreover, there are patients who had extremely progressive diseases after treatment with ICIs [5,6]. Although the mechanisms of resistance are complicated and have not yet been clarified, host factors involving immune-suppressor cells such as regulatory T (Treg) cells, tumor associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs) and their metabolic pathways in the tumor microenvironment (TME) play important roles in resistant to ICIs [7-9]. Metabolic changes are frequently associated with advancement of malignant diseases, and malnutrition is frequently observed as cancer cachexia, which is a multi-factorial

metabolic disorder; it is characterized by hypoproteinemia, a significant reduction of body weight, and disturbance of multiple metabolic pathways, resulting in an imbalance of multiple metabolic regulation [10]. Although causation of cancer cachexia is complicated, host immune factors regulated by a variety of cytokines and chemokines have been reported to be important candidates, as well as multiple immunocompetent cells. Systemic inflammation has been reported to be another essential causative condition of cachexia that induces inflammatory immune reactions resulting in accumulation and proliferation of MDSCs, and is now used as diagnostic criteria of cancer cachexia [11-13]. We have reported that immune function, measured by PHA-stimulated proliferation of lymphocytes (stimulation index: SI), is decreased along with the advancement of cancer, and is significantly inversely correlated with nutritional parameters such as rapid turnover protein (RTP) including prealbumin, retinol binding protein and transferrin. Circulating numbers of MDSCs were significantly elevated in patients with various types of cancer, and these levels were significantly inversely correlated with SIs and RTP levels. Moreover, systemic inflammation measured using a patient's neutrophil-lymphocyte ratio (NLR) have been shown to be associated with levels of MDSCs, as well as inversely to both SIs and RTP levels [14-17]. Although it is well known that Treg cells, TAMs and MDSCs play significant roles in immune suppression in the TME, these cells are also very important in the orchestration of metabolism in TME such as angiogenesis and production of indoleamine 2,3-dioxygenase (IDO) and nitric oxide (NO) towards the escape, progression and expansion of tumor cells. In the present review, we describe the pathological consideration and metabolic characterizations of immune-suppressor cells in TME.

Moreover, these immune suppressor cells recently are a point of focus as one of the metabolic regulators in several non-malignant conditions, such as obesity, diabetes, and pregnancy, and these interesting findings are also described in this review.

1.1 Tumor Associated Macrophages (TAMs, Figure 1)
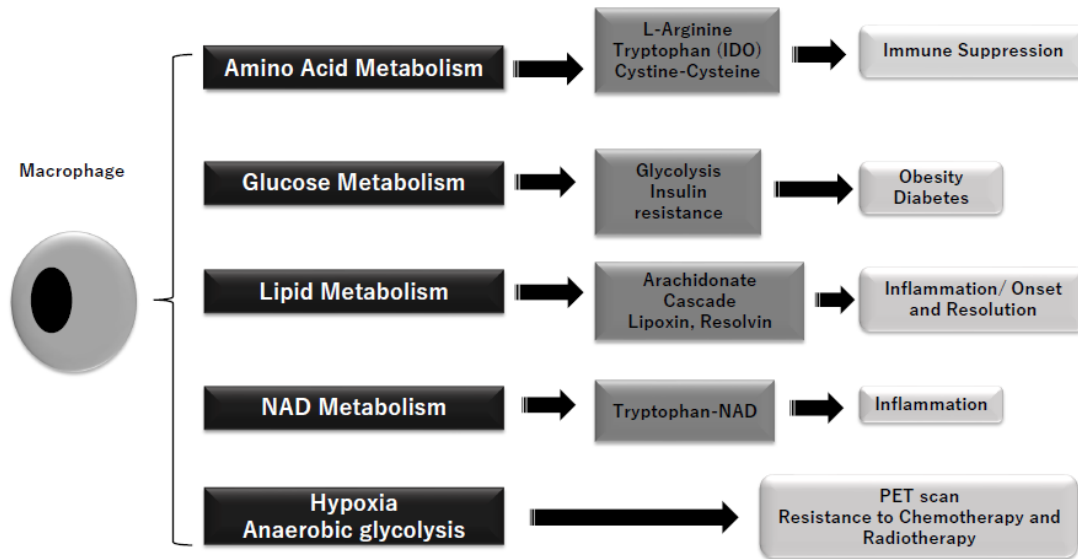
Figure 1: Metabolic action of macrophage

Arginine metabolism (to ornithine and urea) is regulated by macrophages, cystine/cysteine metabolism and tryptophan metabolism with IDO (indoleamine 2,3-dioxygenase) are substantial parts of the immunosuppression related to MDSC (myeloid-derived suppressor cells). Stimulated macrophages (M1) show metabolic shift to anaerobic glycolysis and insulin resistance, and lead to obesity and diabetes. Macrophages are important regulator of inflammation and its resolution. M1 macrophages regulate COX (cyclooxygenase) 1/COX2, leukotriene A4, and thromboxane A, while M2 does arachidonate, COX1 and PGE (prostaglandin)s. Thus, macrophages play important roles in activation and resolution of inflammation. Nicotinamide adenine dinucleotide (NAD), terminal metabolite of tryptophan, shows significant induction of inflammatory cytokines. Macrophages-related hypoxia and anaerobic glycolysis in tumor tissues, typically referred as Warburg's effect is used in PET scan and introduce resistances to chemotherapy and radiotherapy.

Multiple phenotypes of macrophages have long been studied and recently recognized as the result of different microenvironmental stimuli [18]. TAMs have been reported to be closely associated with the regulation of variable important biological pathways related to malignant characterization, including local tumor expansion, tumor cell growth, resistance to chemotherapy and immunotherapy, metastasis, angiogenesis and immunosuppression [19-23]. Biswas and Mantovani reported two distinct phenotypes of macrophages, and named M1 and M2 [24]. M1 macrophages are proinflammatory macrophages,

induced by γ interferon and Toll-like receptor (TLR) ligands, and characterized by the production of proinflammatory cytokines, inducible nitric oxide synthase (iNOS), reactive oxygen species (ROS), polarization of T-helper cell 1 (Th1) responses, and anti-tumor activity. On the other hand, M2 macrophages are induced by IL-4 and IL-13, weaken inflammation, and promote both tumor progression and immunosuppression. A major fraction of macrophages is reported to polarize to M2 during tumor progression. Lipid metabolism is reported to be essential because lipids are important for phagocytosis of macrophages as energy sources and for regulating the membrane fluidity necessary for the phagocytosis mechanism. Macrophages are associated with onset and restoration of inflammation as sources of lipid mediators [25]. M1 macrophages induce cyclooxygenase-2 (COX2) through control of COX1 and the production of leukotriene A4 and thromboxane A, while M2 macrophages upregulate arachidonate 15-lipoxygenase and COX1 [26]. Macrophages also affect the production of prostaglandin E, and can thus profoundly alter their lipid profiles as well as the production of lipid mediators involved in the activation and restoration of inflammation. Type 2 diabetes is a common disorder that causes an increase of blood glucose levels, and has become a global epidemic and a source of huge social and economic costs. Metabolic changes driven by overnutrition and resultant obesity may appear, and resistance to insulin is reported to be closely associated with chronic inflammation [27]. In the adipose tissue of obese individuals, monocytes are recruited and differentiated into M1 macrophages, and may play important immunological roles involved in inflammation [28]. An insulin resistance is established by the orchestration of cells through inflammation [29]. TAMs are characterized by their high expression of M2 markers, and it has been reported that TAMs show high glycolytic activity with high lactate secretion, which is similar to the metabolic features of M1 macrophages [30]. Therefore, although M2 macrophages play important roles in immunosuppression and tumor progression in TME, a differential metabolic regulation of macrophages that is associated with tumors may exist. Hypoxia and aerobic glycolysis are well-known to be resistant factors for antitumor therapies such as chemotherapy and radiotherapy [31,32]. Aerobic glycolysis, known as The Warburg effect, is a form of modified cellular metabolism found in cancer cells, which tends to favor fermentation over the aerobic respiration pathway that most other cells of the body prefer [33]. The Warburg effect is diagnostically the basis for the PET (positron emission tomography) scan, in which an injected radioactive glucose analog is detected at higher concentrations in malignant tumors than in non-cancerous tissues [34]. Jeong et al. reported that TAMs can contribute to tumor hypoxia and glycolysis and the production of TNF-α by TAMs is one of the mechanisms of high glycolysis in cancer cells [35]. It is also reported that intracellular nicotinamide adenine dinucleotide (NAD), which is the final product of tryptophan metabolism, works as a regulator of inflammatory cytokines including TNF-α and IL-6 [24].

1.2 Regulatory T (Treg) cells (Figure 2)

Treg cells control immune reactions to various types of antigens to maintain immune homeostasis. In cancer, Treg cells are involved in tumor development, progression and expansion by suppressing antitumor immunity. Treg cells keep peripheral immune tolerance and work to prevent autoimmune disease on tissue injury when intracellular antigens are exposed to the immune system that may lead to memory of central thymic selection [36]. In cancer, the suppressive

properties of Treg cells can also be established and tumors obtain mechanisms to escape from immune surveillance of a tumor bearing host. The suppression mechanisms have been reported to be variable, including actions to dendritic cells through cytotoxic lymphocyte antigen-4 (CTLA-4), production of inhibitory cytokines, and expression of immune checkpoint molecules such as CTLA-4, inducible T-cell co-stimulator (ICOS), and lymphocyte activation gene-3 (LAG-3) [37]. Metabolic characterization in the TME is determined by a depletion of glucose, glutamine and tryptophan and enrichment of lactic acid and kynurenines [38]. There are metabolic differences between CD8+ T cells and Treg cells. CD8+ T cells utilize aerobic glycolysis primarily whereas Treg cells use oxidative phosphorylation (OXPHOS), which is

another mechanism of immune suppression and resultant tumor growth in the TME. IDO is an essential enzyme in the kynurenine pathway of tryptophan metabolism. Depleted levels of tryptophan in the tumor microenvironment and cause T cell dysfunction [39]. The IDO-dependent catabolism subsequently induces the generation of Treg cells through inhibition of IL-6 production by DCs [40]. Recent investigations have revealed that T cell responses are suppressed by nutritional conditions of the TME, such as glucose, amino acids and fatty acid. Furthermore, hypoxia is: commonly seen in tumor tissue and HIF-1 alpha; upregulated in hypoxia; a negative regulator of Treg cells differentiation; and essential for suppression activity of Treg cells [41,42].
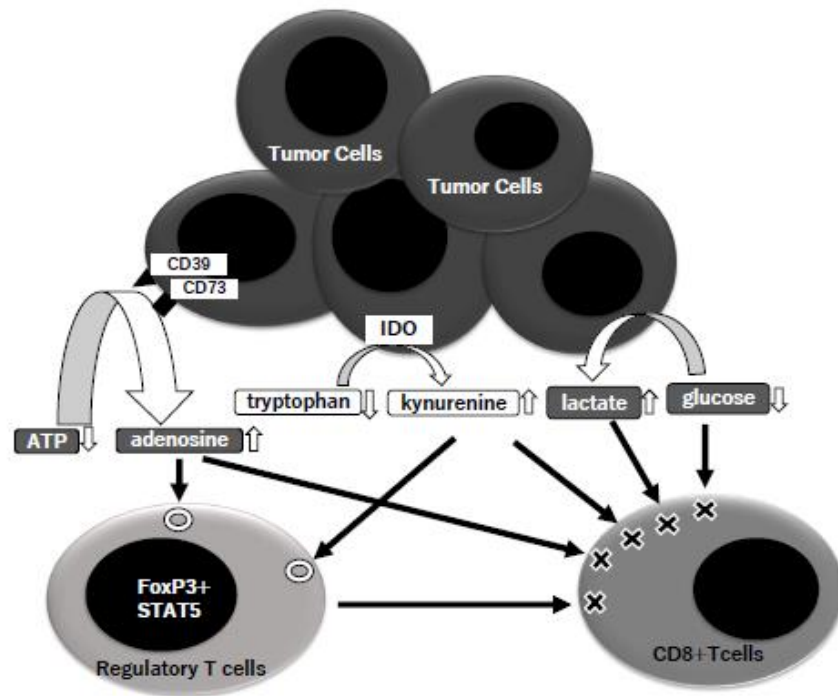

Figure 2: Metabolic actions of Treg.

The molecules of CD39 and CD73 on tumor cells metabolize extracellular ATP to adenosine, and IDO (indoleamine 2,3-dioxygenase) does tryptophan to kynurenine. Tumor cells consumes glucose and induce accumulation of lactate. The steps of these metabolism in TME (tumor microenvironment) induce an enhancement of Treg and suppression of

CD8+T cells.

1.3 Myeloid-derived suppressor cells (MDSCs, Figure 3)
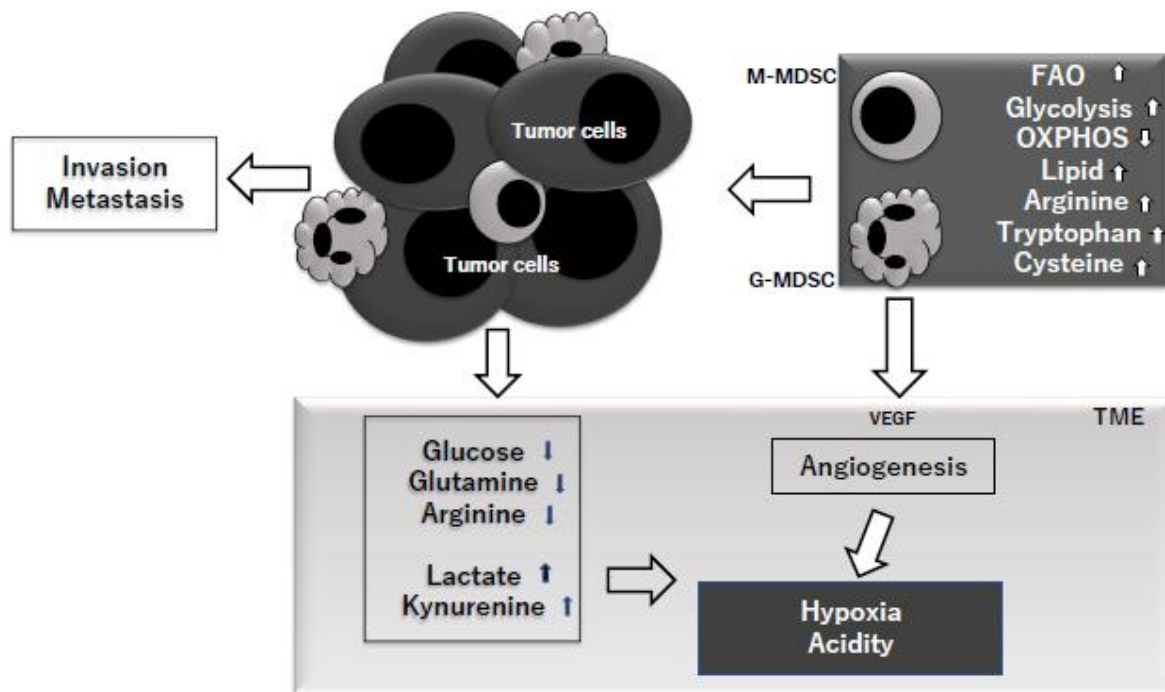
Figure 3: MDSC in the TME (tumor microenvironment) upregulate fatty acid oxidation (FAO), glycolysis and downregulate oxidative phosphorylation (OXPHOS). They also increase accumulations of lipid, tryptophan and cysteine and in TME, the concentrations of glucose, glutamine and arginine are decreased, while those of lactate and kynurenine are increased. VEGF (vascular endothelial growth factor) produced by tumor cells, MDSC and other cells including Treg is produced and lead to angiogenesis which enhance hypoxia and resultant acidity. These entire metabolic background can enhance tumor invasion and metastasis.

MDSCs are observed in most patients with cancer, where MDSCs infiltrating cancer tissue orchestrate many immunocompetent cells toward immunosuppression and resultant cancer escape. Prosperous studies on MDSCs have been performed in cancer patients during past decade and reported that MDSCs is the biggest obstacle for successful cancer immunotherapies [43]. The induction and expansion of MDSCs is clearly associated with chronic inflammation in cancer patients. Although normal inflammatory response after infectious diseases or trauma is self-limiting, the chronic inflammation in cancer patients develops different characterizations including immunosuppression, hypoxia and tumor progression [44]. In addition to developing solid status of immune suppression via induction of other immune suppressing cells such as Treg cells, MDSCs induce strong metabolic alterations toward immunosuppression and tumor expansion in the TME. It was reported that MDSCs produce reactive oxygen species (ROSs), which are not only toxic to tumor-infiltrating lymphocytes but also proliferate MDSCs

[44]. An increased production of ROS upregulates the expression of VEGF (vascular endothelial growth factor) on MDSCs, and suppressed production of ROS induces the differentiation of MDSCs to macrophages or DCs. MDSCs also produce reactive nitrogen species (RNS) and nitric oxide (NO), and increased levels of NO induce the expression levels of cyclooxygenase 2 (COX-2) and HIF-1alpha, resulting in high production of prostaglandin-E2 (PGE2) and VEGF. PGE2 has been reported to upregulate the expressions of IDO, IL-10, and arginase. The decreased levels of L-arginine by arginase produced by MDSCs can be a cause of apoptosis of T lymphocytes via inducible nitric oxide synthase (iNOS) and block T cell activation [45]. MDSC in the TME have been reported to show upregulation of fatty acid oxidation (FAO), glycolysis, increased uptake of lipid, arginine, tryptophan and cysteine, and decreased oxidative phosphorylation (OXPHOS). It has been reported that, in TME, the levels of glucose, glutamine and arginine are decreased and those of lactate and kynurenine are increased. Thus, the TME became thus to be hypoxic and acidic [46]. It has been reported that, in cancer patients, elevated body mass index (BMI) is unexpectedly associated with longer survival, the so called "obesity paradox" [47]. However, there are solid data that tumors grow more rapidly and the survival is worse in obese patients than in non-obese patients. Moreover, excess weight is associated with increased cancer risk, morbidity and mortality in young adult patients with cancer [48]. MDSCs are frequently found in adipose tissue with the presence of pro-inflammatory mediators such as IL-6, IL-1β, TNF-α and PGE2, which are major inducers of MDSCs [49]. Obesity is frequently associated with metabolic dysfunction such as increased blood sugar levels. It has been demonstrated that obesity-driven MDSCs protect against an increase of glucose levels and insulin tolerance [49]. It is well

known that chronic inflammation is closely related to aging. Franceschi reported that increased proinflammatory status is a distinctive feature of aging, and named chronic inflammation via continuous antigenic load and stress "inflamm-aging" [50]. Aging-associated pathogenesis such as atherosclerosis, Alzheimer's disease, osteoporosis and diabetes mellitus are closely related to chronic inflammation. Since the numbers of MDSCs in bone marrow, peripheral blood, spleen and lymph nodes increase with age [51,52], increased immunosuppression and carcinogenesis among older individuals may be caused by inflamm-aging-driven MDSCs. Myelopoiesis increases along with aging, and its process has been reported to be regulated by TGF-β produced by MDSCs. Salminen et al. reported that this age-related growth of MDSCs may result in immunosenescence and destruction of host tissue appearing in older individuals [53,54]. As beneficial functions of MDSCss, one important point regarding pregnancy may be picked up in this review. MDSCs facilitate implantation and protect the allogeneic early embryo from immune-mediated rejection [55]. The insufficient tolerance can lead to severe complications such as preterm birth and fetal growth retardation and therefore tolerance is important during pregnancy. Although maternal-fetal tolerance was studied and helper T 2 cells (Th2 cells) were the major factor, another complicated mechanism involving MDSC has recently been reported to exist [56,57]; it was reported that the number of MDSC is significantly increased in the circulating blood of pregnant women compared to non-pregnant women, and especially high in the placenta in comparison with maternal and fetal blood [56,57]. The mechanisms of immune tolerance involving MDSCs are: inhibition of T-cell function via expression of arginase, iNOS, and IDO; polarization of Th2-response [58,59], and inhibition of NK cell function via

downregulation of NKG2D receptor in NK cells.

2. Conclusions and Future Directions

Metabolic impacts in the TME play a crucial, although not fully understood, role in resistance to ICIs. As MDSCs in the TME exist. Among them, hypoxia, angiogenesis and chronic inflammation are important host factors to be considered when therapeutic approaches combined with ICIs are tried. Moreover, cancer immunotherapies tailored with metabolic characterizations such as parameters of hypoxia, inflammation or obesity may be needed for the establishment of successful treatment modalities against cancer in the immunotherapy era.

Conflict of interest

All of the authors declare that there is no conflict of interest regarding this article.

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