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Immunometabolism: A novel perspective of liver cancer microenvironment and its influence on tumor progression

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Abstract

The initiation and progression of liver cancer, including hepatocellular carcinoma and intrahepatic cholangiocarcinoma, are dependent on its tumor microenvironment. Immune cells are key players in the liver cancer microenvironment and show complicated crosstalk with cancer cells. Emerging evidence has shown that the functions of immune cells are closely related to cell metabolism. However, the effects of metabolic changes of immune cells on liver cancer progression are largely undefined. In this review, we summarize the recent findings of immunometabolism and relate these findings to liver cancer progression. We also explore the translation of the understanding of immunometabolism for clinical use.

Key words: Cholangiocarcinoma; Hepatocellular carcinoma; Tumor microenvironment; Local immune status; Metabolite

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Core tip: The liver microenvironment provides a special place for initiation and progression of liver cancer, in which immune cells play a vital role. On the one hand, immunosuppression leads to tumor survival and progression; on the other hand, the instigation of tumor metabolites and signal molecules to immune cells makes the state of immunosuppression further strengthened. Intensive studies of the metabolic state of immune cells in the tumor microenvironment is beneficial to our understanding of the regulation of pro-tumor patterns, and to provide theoretical basis

and guidance for immunometabolic therapies for liver cancer.

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INTRODUCTION

Liver cancer is one of the most common malignancies and has the third leading mortality rate and seventh leading incidence rate worldwide^[1]. To date, with over 42000 cases diagnosed and 30000 deaths in the United States per year, a continuous increase in both morbidity and mortality is observed in liver cancer^[2]. Unfortunately, the prognosis of advanced liver cancer is still poor despite the many treatments that have been developed in the past few decades. Thus, novel approaches to treat liver cancer are urgently needed.

The tumor microenvironment (TME) plays critical roles in tumor development and is characterized by complicated components, including various types of non-tumoral cells and non-cellular materials^[3]. TMEs can be largely distinct among different types of cancers and among different patients with the same type of cancer. Within a patient, the TME can consistently change as the tumor progresses and is influenced by the physiopathological conditions of the patient. Thus, it is theoretically impossible to identify the precise state of the TME. However, under certain conditions, the TME can be specialized to show typical traits, and in particular, this specialized TME may affect tumor progression. Understanding these particular TMEs, if not all of them, can outline the crosstalk between the TME and tumor cells and facilitate the development of novel strategies for tumor treatment^[4].

Pathologically, liver cancer mainly includes hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC). The two types of liver cancers share a similar hepatic microenvironment, but may have different TMEs due to the various biological characteristics of the tumor cells. For instance, in a considerable proportion of cases, ICC harbors isocitrate dehydrogenase (IDH) 1 and IDH2 mutations^[5], which are rare in HCC^[6]. IDH1 and IDH2 are important enzymes involved in cellular metabolism. Therefore, IDH1/2 mutations can substantially influence the metabolite profiles in cells and TMEs. In this case, the roles of the TME in liver cancer progression may be greatly altered. However, knowledge in this field is poor and scattered.

Immune cells are key players in liver cancer progression, and their recruitment and functions are

profoundly affected by the TME^[7]. Other molecules in the TME, such as fatty acids and glucose, are able to regulate the metabolism, phenotype and function of immune cells^[8,9]. The term "immunometabolism" has recently been proposed and indicates the functional intracellular metabolic alterations that occur within immune cells^[10]. These affected immune cells, in turn, could have significant effects on adjacent tumor cells. In this minireview, we collected evidence of TME heterogeneity resulting from the different biological features of cancer cells and functional changes of immune cells resulting from an altered TME and how the TME affects tumor progression *via* metabolically regulated immune cells.

CHARACTERISTICS OF IMMUNE CELLS IN LIVER CANCER MICROENVIRONMENT

With genetic and epigenetic changes, hepatoma cells express specific tumor-associated antigens, such as α -fetoprotein (AFP), glypican-3 (GPC3) and melanoma-associated gene-A1 (MAGE-A1), which can be taken up by antigen-presenting cells and presented to T cells, resulting in a cytotoxic reaction to eliminate cancerous cells^[11,12]. However, immunosuppressive factors and immune-inhibitory checkpoint molecules inhibit anti-tumor reactions and create a special microenvironment to facilitate tumor progression^[12]. Almost all types of immune cells are deeply involved in the TME of liver cancer (Figure 1), including macrophages, Kupffer cells, neutrophils, T cells, B cells, innate lymphoid cells (ILCs), dendritic cells (DCs), natural killer (NK) cells, natural killer T (NKT) cells, and myeloid-derived suppressor cells (MDSCs)^[13-18].

Macrophages and neutrophils

Macrophages display remarkable heterogeneity in liver cancer for various reasons, such as the cell origin (resident Kupffer cells and recruited monocyte-derived macrophages), stimulating signals (*i.e.*, microbes, cell debris) and functional phenotype (*i.e.*, inflammatory, anti-inflammatory). Notably, macrophages can play two or more contradictory roles in a particular TME. As guardians, macrophages are normally activated by inflammatory signals and together with CD4⁺ T cells eliminate precancerous senescent cells^[19]. Kupffer cells directly show cytotoxicity against tumor cells^[20-22]. In addition, macrophage-derived interleukin (IL)-12 hampers tumor progression by activating NK and NKT cells^[23,24]. As an accomplice, however, tumor-associated macrophages (TAMs, most of which are M2-polarized macrophages), induced by IL-4 and tumor growth factor (TGF)- β , accumulate in liver cancer and are correlated with the poor prognosis of patients^[25,26]. Importantly, these macrophages express the immune checkpoint protein programmed cell death-ligand 1 (PD-L1, also known as B7-H1), which inactivates CD8⁺ T cells^[13,27,28]. *Via* other immunosuppressive signals,

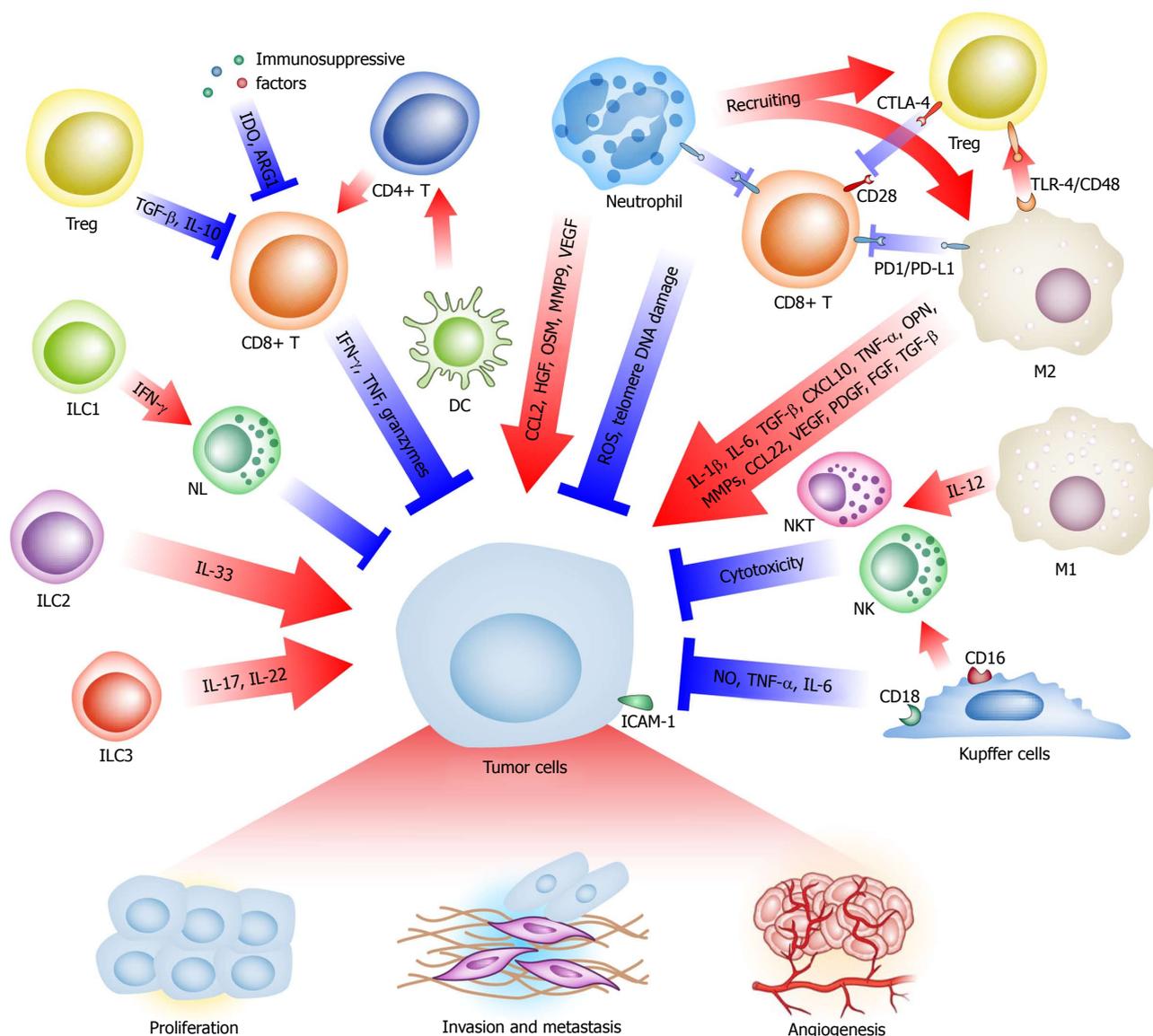


Figure 1 The immune cells in the tumor microenvironment regulate liver cancer progression. Many types of immune cells in the TME show pro- or anti-tumoral effects on the liver cancer cells by cell-specific mechanisms. Complicated crosstalk between immune cells is also common. TME: Tumor microenvironment; ILC: Innate lymphoid cell; NKT: Natural killer T.

such as Toll-like receptor (TLR) 4 and CD48/2B4, M2-polarized macrophages promote the recruitment of regulatory T cells (Tregs) and suppress the activity of NK cells^[29-31]. Moreover, these macrophages can secrete various tumor proliferation-promoting cytokines, such as IL-1 β , IL-6, TGF- β , C-X-C motif chemokine (CXCL) 10, invasion and metastasis-promoting factors like tumor necrosis factor (TNF)- α , osteopontin (OPN), matrix metalloproteinases (MMPs), C-C Motif chemokine ligand (CCL) 22, and proangiogenic growth factors, like vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), fibroblast growth factor (FGF), and TGF- β , to build a tumor-prone inflammatory microenvironment^[3,26,32-35].

Similar to macrophages, neutrophils also have diverse functions at different stages of liver cancer progression. In the case of a hepatic infection or injury, neutrophils

gather at the wound site together with macrophages to eliminate pathogens and necrotic materials. Additionally, neutrophils stimulate reactive oxygen species (ROS) and telomere DNA damage in hepatocytes, mediating neoplasia and progression^[36]. Mirroring macrophage plasticity, a pro-tumoral phenotype of tumor-associated neutrophils (TANs) is proposed^[37,38]. Despite biomarkers of this subtype, immunosuppression is the most central function of TANs. The immunosuppressive molecule PD-L1 is regularly displayed in TANs^[39] and recruits macrophages and Treg cells to the liver cancer TME and induces impaired anti-tumoral immunity^[14]. The infiltrating TAN density and neutrophil-lymphocyte ratio is reported to be a predictor of outcome, chemotherapy resistance, and recurrence risk^[40-42]. Furthermore, neutrophils promote tumor progression by secreting cytokines and other functional molecules, such as CCL2

for tumor growth, hepatocyte growth factor (HGF) and oncostatin M (OSM) for metastasis, and MMP9 and VEGF for angiogenesis^[38,43-47].

T cells

CD8⁺ T cells are the most important executors of adaptive immunity against neoplasms, including liver cancer. Unfortunately, the TME transforms these 'warriors' into 'servants'. Compared with the normal liver, tumor tissue has a lower density of CD8⁺ T cells and a higher density of Tregs. The ratio of CD8⁺ T cells to Tregs typically indicates a poor prognosis^[48-50]. Recent studies suggest that interferon (IFN)- γ , TNF and granzyme secretion by CD8⁺ cytotoxic T lymphocytes (CTLs) represent a common cytotoxic reaction against tumors^[51,52]. Tregs, characterized by CD4, CD25, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and forkhead box P3 (FoxP3) expression, can eliminate IL-2 *via* its receptor subunit CD25, downregulate CD80 and CD86 and conjugate to the co-stimulatory molecule CD28 competitively with CTLA-4 to suppress immune responses. In addition, Tregs secrete TGF- β and IL-10 into the TME to suppress T effector cells^[52]. *Via* a complicated regulatory network, several subtypes of T cells contribute to the immunosuppressive TME.

ILCs

ILCs are recently identified innate immune cells that lack a specific antigen receptor. These cells originate from mucosal-associated lymphoid tissues and act as a sentry of the rapid immune response and regulator of immune homeostasis and inflammation^[53]. Mirroring the classification of helper T cells (Th), ILCs are divided into three classes. ILC1s produce Th1-associated cytokines, ILC2s are associated with Th2-associated cytokine release, and ILC3s secrete Th17-associated cytokines^[54]. As these three components simultaneously exist in the liver, they are likely to be involved in hepatocarcinogenesis and progression. ILC1s produce IFN- γ to activate NK cells and indirectly participate in cancer immunosurveillance, while ILC3s release IL-17 and IL-22, which may promote tumor growth and angiogenesis^[16,55,56]. Moreover, we observed an increasing number of ILC2 in HCC tissue (unpublished data) and an elevated level of IL-33 in both serum and tumor tissue samples from HCC patients^[57]. IL-33 can stimulate rapid growth and metastatic progression in breast cancer and cholangiocarcinoma^[58,59]. Therefore, the initiation and growth of liver cancer promoted by the ILC2-related IL-33/ST2 axis might be theoretically tenable^[60].

the survival of tumor cells seems to be in question. However, the tumor is able to reprogram the cellular metabolism for neoplastic proliferation. The abnormal metabolism induced by cancer provides energy and metabolites for cell activity and additionally modifies many related pathways that influence various biological processes^[61].

General alterations

The liver is a metabolic organ, and metabolic disruption of the liver can lead to spontaneous hepatocarcinogenesis^[62]. The principal metabolic alterations in the liver cancer were profiled by metabolomics analysis, which showed elevated glycolysis, gluconeogenesis and β -oxidation, with reduced tricarboxylic acid cycle (TCA cycle) activity^[63,64]. Aerobic glycolysis, also known as the "Warburg effect", is frequently observed in various tumors. This theory indicates that tumor cells predominantly use glycolysis, even in the presence of sufficient oxygen^[65]. For liver cancer, glycolysis also plays a dominating role in glucose metabolism^[63]. Accumulating studies have revealed that glycolysis is associated with genetic and epigenetic changes. Activated oncogenes and mutant tumor suppressors are associated with glycolysis. Glucose transporters (GLUTs), glycolysis-related enzyme hexokinase2 (HK2), pyruvate kinase M2 (PKM2), and lactate dehydrogenase (LDH) A are also overexpressed in liver cancer tissue, suggesting an increased glycolysis activity^[66]. Moreover, the hypoxic TME and overexpression of β -catenin in liver cancer stabilize hypoxia inducible factor (HIF)-1 α to activate glycolytic enzymes^[67-70].

Fatty acid β -oxidation is enhanced in liver cancer to overcome the energy shortage and reduce tumor dependence on glucose. Metabolic alteration increases FA biosynthesis and glycerolipid metabolism, leading to fatty acid and lipid accumulation^[71,72]. However, the alterations of various types of fatty acids are complicated. Additionally, almost all amino acids are increased in liver cancer due to the reduction of amino acid catabolism^[63]. Although these general changes were identified, many other factors may influence the levels of metabolites in TME.

Involvement of specific mutations

Some specific mutations profoundly change the metabolism of liver cancer. The Tumor Cell Genomic Atlas (TCGA) project of HCC demonstrated that IDH and fibroblast growth factor receptor (FGFR) are meaningful mutations in HCC. IDHs are critical enzymes for cell metabolism, particularly the TCA cycle. IDH1/2 mutations convert α -ketoglutarate (α -KG) into 2-hydroglutarate (2-HG)^[73]. The unusually decreased ratio of α -KG/2-HG can significantly influence tumor cell biology by competing with α -KG and regulating epigenetic expression^[74]. However, overproduced 2-HG by tumor cells can also be released into the TME since elevated serum and urinary levels of 2-HG can

ALTERED METABOLISM OF LIVER CANCER AND ITS INFLUENCE ON THE TUMOR MICROENVIRONMENT

With their rapid growth and limited nutrition supply,

be detected in patients with IDH1/2-mutated solid tumors^[75,76]. Although 2-HG seems to be impermeable, this enzyme acts on stromal cells within the bone marrow microenvironment through an ROS/extracellular signal-regulated kinase (ERK) signaling pathway^[77], suggesting that 2-HG may influence immune cells in the TME of liver cancer. This finding is important since IDH-like HCCs (particularly those containing IDH1/2 mutations and those with IDH-like gene expression) are indicative of worse clinical outcomes for undefined reasons^[6]. In addition to 2-HG, IDH-like HCCs and IDH1/2 mutated ICCs have other significant metabolic alterations, such as gliomas due to pseudohypoxia, an interrupted Krebs cycle, and epigenetic changes^[78]. In addition, IDH gain-of-function mutations also induce the reprogramming of pyruvate and lipid metabolism to maintain cell proliferation and clonogenicity^[79,80]. Therefore, the TMEs of these tumors likely have distinct features, and the immune cells within such TMEs may be reprogrammed to have different functions.

FGFR genetic aberrations include mutations, amplifications, and gene fusions, which have been observed in over 10% of liver cancer^[81-83]. FGFR2 fusions are active kinases with the highest incidence^[84]. These genetic aberrations indirectly affect glucose and lipid metabolism by activating the kinase network^[85]. Additionally, the oncogenic FGFR3-transforming acidic coiled-coil containing protein (TACC) 3 fusion activates oxidative phosphorylation and mitochondrial biogenesis, causing a mitochondrial respiration-dependent subtype of tumor cell^[86].

Influence of hepatic viruses

Hepatitis viruses, particularly HBV in eastern countries and HCV in western countries, cause specific metabolic alterations during hepatocarcinogenesis and tumor progression. Hepatic virus infections activate many abnormal signaling pathways, which cause aberrant functions and expression of metabolism related enzymes^[87]. As a consequence, HBV infection in patients is associated with increased free fatty acids (FFAs) and acyl-carnitines and decreased triglycerides, phospholipids, and sphingomyelins^[88]. Thus, in the TME of HBV-related liver cancer, the increased FFAs and decreased glucose may result from increased β -oxidation and glycolysis, respectively. HBV-related inflammation can stimulate the expression of HIF-1 α through the PI3K/AKT and mitogen-activated protein kinase (MAPK)-Ras-Raf pathways. The latter up-regulates GLUT1 and glycolytic enzymes, increases the glycolytic flow, and induces ROS accumulation. These alterations eventually cause DNA oxidative damage and malignant transformation^[89-92]. HBx activates the adenosine 5'-monophosphate-activated protein kinase (AMPK) and fatty acid oxidation (FAO) pathways as well as the HBx-LXR α -SREBP1/FAS pathway, which allows HCC cells to survive under metabolic stress^[93-95]. HCV establishes an insulin-resistant TME in the liver through several

mechanisms^[96,97]. For instance, HCV protein can induce the overexpression of protein phosphatase 2A (PP2A), which dysregulates hepatic glucose homeostasis by inhibiting AKT and the dephosphorylation of FoxO1^[98]. However, the molecular mechanism of viral hepatitis-related metabolic alternations is not well understood. HBV integration into the tumor suppressor gene region causes metabolic alterations. Signaling molecules, such as TGF- β , mammalian target of rapamycin (mTOR), Smad3, and c-Myc, are activated by HBV and HCV, which is closely correlated with tumor progression^[87,96].

Participation of other concomitant diseases

Liver cancer has a higher incidence in people with chronic non-infectious liver diseases. Therefore, the metabolic changes of liver cancer are related to cirrhosis and nonalcoholic fatty liver disease (NAFLD), which typically includes lipid anomalies, particularly dysregulated *de novo* lipogenesis^[99]. For instance, peripheral insulin resistance together with enhanced mitochondrial β -oxidation and oxidative stress are the most prominent features of NAFLD and nonalcoholic steatohepatitis (NASH)^[100]. Thus, NAFLD-related liver cancer is associated with elevated oxidative metabolism and amplified anaplerosis/cataplerosis^[101]. With the increasing content of hepatic FFAs, liver cells may endure a mild respiratory dysfunction. The increasing import of FFAs into the mitochondria is accompanied by an elevated rate of β -oxidation. The overloaded fatty acid β -oxidation triggers the subsequent accumulation of ROS, which further leads to lipid peroxidation and severe mitochondrial oxidative damage^[102,103]. These strong oxidizing products promote inflammation, fibrosis, and even carcinogenesis. Lipid metabolism shows an alteration from β -oxidation to ω -oxidation during liver cirrhosis^[104]. Intriguingly, a metabolic switch from oxidative phosphorylation to glycolysis in hepatocytes in early-stage cirrhosis may satisfy the extreme energy requirements under such conditions^[105]. This evidence demonstrates that concomitant liver diseases or even systemic metabolic diseases, such as diabetes mellitus, can influence the function of immune cells and their functions in promoting tumor progression.

Metabolic reprogramming of local immune cells in liver cancer

The role of metabolism in regulating immune cells has recently aroused general concerns. Evidence collected in several types of solid tumors indicated the importance of tumor immunometabolic reprogramming and suggested a novel and crucial area for future research of liver cancer^[106]. The complicated crosstalk between metabolically reprogrammed immune cells and liver cancer cells has been suggested, but the molecular mechanisms need further exploration (Figure 2).

Because they exist at a considerable quantity, macrophages play a leading role in the crosstalk between liver cancer cells and immune cells. The

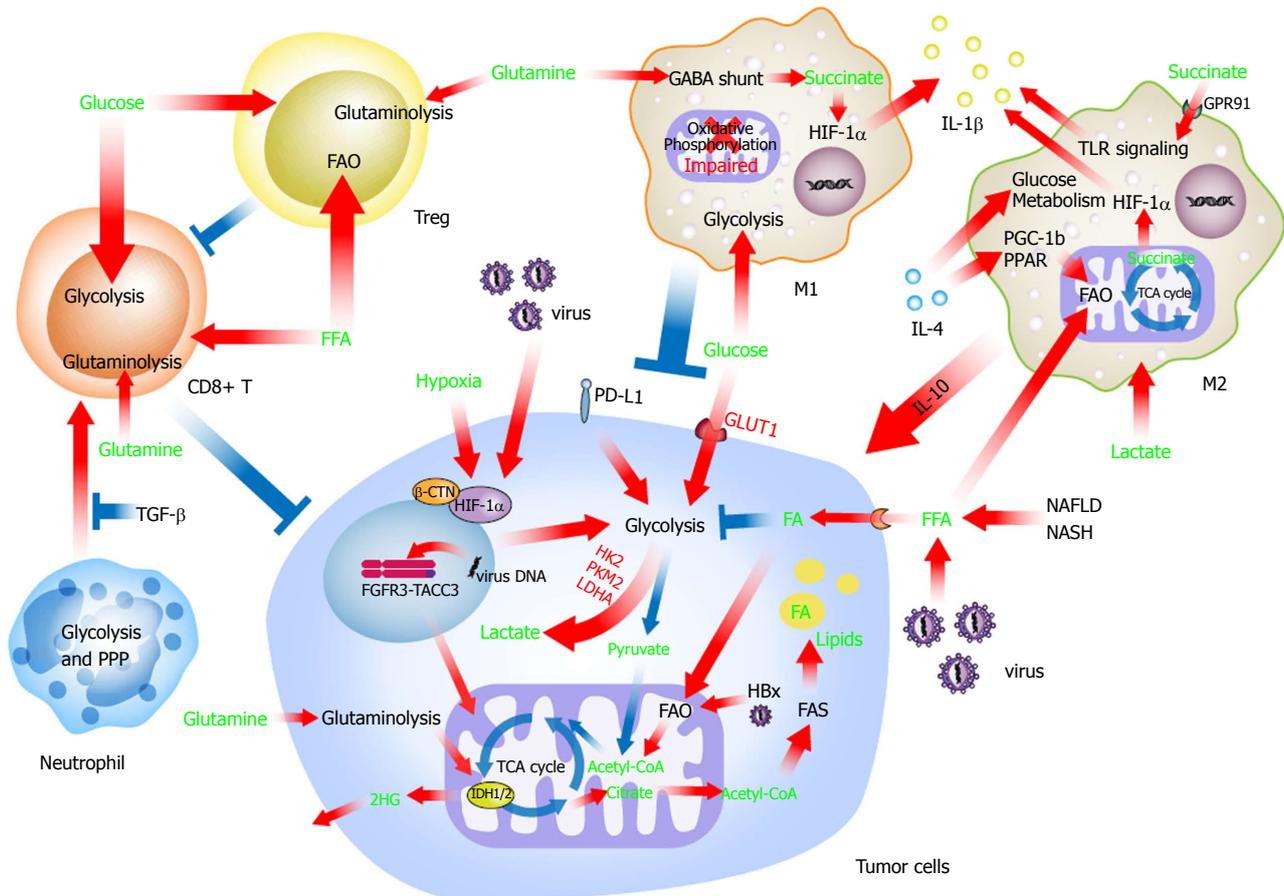


Figure 2 Metabolites in the tumor microenvironment affect the anti/pro-tumoral functions of immune cells. Energy resources including glucose, glutamine, free fatty acids, and other metabolites such as succinate largely alter the functions of macrophages, neutrophils, and T cells. These metabolically reprogrammed immune cells then have a differed influence on the liver cancer cells compared to the original immune cells. FAO: Fatty acid oxidation.

phenotypes and functions of macrophages are hot topics in the field of immunometabolism. Professor O' Neill's group and other investigations have conducted several pioneering and important studies to decipher macrophage immunometabolism. Recent evidence has suggested that the energy source (*e.g.*, glucose and fatty acids) participates in the determination of macrophage polarization^[107,108]. However, the role of FAO in the alternative activation of macrophages is still under debate. Huang *et al.*^[108] initially demonstrated an essential role for FAO in the alternative activation of mouse macrophages, while two groups in Germany and the United States subsequently provided convincing evidence that FAO was indispensable for the M2 polarization of human and mouse macrophages, respectively^[109,110]. This discrepancy may partially reflect differences between mouse and human macrophages and the potential off-target effects of etomoxir (a carnitine palmitoyltransferase I A, CPT1A inhibitor used to inhibit FAO by some researchers). Although the role of FAO in macrophage activation has not yet been determined, FAO enhances the functions of M2 polarized macrophages^[111].

Generally, M2 polarized macrophages use oxidative phosphorylation, FAO in particular, to obtain the

required energy and exert pro-tumor function in various scenarios, including liver cancer^[108,112,113]. Mechanistically, IL-4 induces the expression of peroxisome proliferator-activated receptors (PPAR) and PPAR gamma coactivator 1-beta (PGC-1b), which orchestrate alteration of FAO as well as mitochondrial respiration^[114]. Similar to liver cancer cells in a background of chronic fatty liver disease, FFA accumulation attenuates mitochondrial respiration and increases FFA uptake *via* CD36, resulting in a predominant FAO mode in macrophages^[115,116]. In addition, IL-4 signaling also increases glucose metabolism by the AKT/mTOR pathway^[117-119]. Lactic acid produced by liver cancer cells through glycolysis is another non-negligible issue when considering the metabolic reprogramming of liver cancer-associated macrophages. The polarization of macrophages to an immunosuppressive and pro-tumoral phenotype is mediated by lactic acid *via* a different, as yet unidentified pathway^[119-121] in liver cancer. M2 polarized macrophages also take up insulin growth factor 1 for a self-immunometabolic reprogramming, leading to reduced phagocytosis and lower energy expenditure^[122], which may consequently regulate liver cancer progression.

However, M1 polarized macrophages have enhanced glycolytic metabolism and impaired oxidative phosph-

orylation through the AKT/mTOR/HIF-1 α pathway^[123]. This association is consistent with the fact that many glycolytic enzymes facilitate inflammatory cytokine production. For example, PKM2, which is critical for glycolysis, activates HIF-1 α and induces IL-1 β production^[124]. Although under some conditions, FAO was also found to support inflammasome activation in M1 polarized macrophages by regulating CPT1A activity^[125,126].

Other metabolites in the TME can also influence the phenotype and function of macrophages. Succinate is a known inflammation inducer of macrophages. Succinate enhances IL-1 β secretion *via* succinate receptor 1 (SUCNR1, also known as GPR91)-mediated amplification of TLR signaling^[127]. In addition, intracellular succinate, derived from the γ -aminobutyric acid (GABA) shunt and anaplerosis of α -KG upon stimulation of TLR4, enhances IL-1 β production through the repurposing of mitochondrial function from ATP production to ROS generation^[128,129].

Neutrophils are metabolically similar to M1 polarized macrophages and rely on aerobic glycolysis and the pentose phosphate pathway (PPP) as their principal mode of energy metabolism, by which the formation of neutrophil extracellular traps produces biological effects^[130].

During differentiation, a switch from FAO to glycolysis and glutaminolysis triggers the maturation of T effector cells^[131]. The rapid supply of ATP helps CTLs to meet their increasing bioenergetic and biosynthetic requirements^[132]. Nevertheless, glucose shortage and lactic acid abundance limit the function of CTLs, and the enhancement of FAO preserves the cytotoxicity of CTLs in tumors^[133]. By contrast, Treg cells favor FAO rather than glycolysis, by which these cells survive in the persistent low-glucose and hypoxic tumor microenvironment and suppress the tumor-killing function of CTLs^[131,134]. Moreover, Treg cells rely on oxidative phosphorylation for energy supply, on FAO for cell differentiation, and on glutaminolysis for cell proliferation^[134,135]. Taken together, these observations demonstrate that environment-related metabolism regulates the anti- and pro-tumor functions of tumor-infiltrating lymphocytes.

INFLUENCE OF REPROGRAMMED IMMUNE CELLS ON LIVER CANCER PROGRESSION

Immunometabolic reprogramming has a dual-function in tumor progression. Typically, M1 polarized macrophages facilitate inflammation and the antitumor response *via* elevated glycolysis, while M2 polarized macrophages play an FAO predominant role, secreting IL-10 to suppress the immune reaction. The switch in the metabolism of TAMs leads to an ample signaling transition by which these cells suppress immune reactions (by presenting PD-1, *etc.*), accelerate tumor proliferation (by releasing TNF, Wnt signals, *etc.*), promote angiogenesis (by secreting VEGF,

FGF2, *etc.*), and enhance tumor invasion and metastasis (by MMP9, TGF- β , *etc.*)^[26,136]. We further revealed that IL-1 β facilitated epithelial-to-mesenchymal transition and subsequent metastasis in liver cancer, and this effect was mediated by a group of pro-inflammatory M2-like TAMs with an up-regulated level of glycolysis^[137]. Interestingly, the function of TANs is opposite that of TAMs under different circumstances. For instance, the absence of TGF- β leads to a TANs-induced anti-tumor response by CTLs, whereas this situation is completely different in the presence of TGF- β ^[37].

The influence of metabolic reprogramming on lymphocytes differs in the presence of high functional heterogeneity. CTLs enhance glycolysis, glutaminolysis, and even FAO to exert anti-tumoral cytotoxicity, while CD4⁺ T cells develop into two phenotypes with contrary functions. With a similar switch characterized by up-regulated glycolysis as well as increased glutaminolysis and PPP, Th1 cells induce macrophage- and NK cell-related anti-tumoral responses, whereas Th2 cells induce immunosuppressive reactions^[113].

PERSPECTIVES OF LIVER CANCER THERAPY FROM IMMUNOMETABOLISM

Theoretically, it is feasible to target metabolic enzymes or metabolites in immune cells for therapeutic purposes. Indeed, several cancer-related immunometabolic molecules are suitable as potential targets for drug development (Table 1).

Considering carbohydrate metabolism, glycolysis is important to activated immune cells. Inhibition of HIF-1 α can attenuate TAM/TAN-mediated IL-1 β secretion, reduce hypoxic adaptation of tumor cells, and regulate the differentiation and function of lymphocytes^[137,138]. The regulation of PI3K signaling by PTEN in immune cells may also show some effects on macrophage activation and Treg cell function with a concurrent influence on glycolysis^[139,140].

The mTOR pathway may be a suitable target to regulate immune cells by manipulating cellular lipid metabolism. Inhibition of mTOR by rapamycin can block the development of macrophages and CD4⁺ T cells in several scenarios, including liver cancer^[141,142]. Moreover, FAO plays a predominant role in the metabolism of M2 polarized macrophages. Hence, inhibition of FAO by etomoxir or other methods (*e.g.*, targeted delivery of CPT1A siRNA/shRNA) may limit the immunosuppressive function of M2 macrophages. However, in a resource-deficient microenvironment, CTLs also take up FFA and exert cytotoxicity; thus, the selective increase of FFA import to CTLs enhances the anti-tumoral capacity of these cells^[133]. It is also feasible to target proteins that play central roles in metabolic pathways (*i.e.*, iNOS, PKM2, Foxp3, *etc.*). The difficulty of this strategy is that targeting should be cell specific because the same metabolic pathway can have diverse effects on different

Table 1 Immunometabolic therapies for cancers

Targets	Agents	Mechanisms	Developments
PKM2	DASA, TEPP46	Inhibition of HIF1 α	Preclinical
HIF1 α	PX-478, RO7070179, EZN-2968	Inhibition of HIF1 α	Phase 1
PTEN	VO-Ohpic, SF1670	Inhibition of PI3K	Preclinical
PDK	Dichloroacetate	Inhibition of glycolysis	Phase 2
GLUT1	Ritonavir	Inhibition of glycolysis	FDA-Approved
LDH	Gossypol (AT-101), FX11, Galloflavin	Inhibition of glycolysis	Phase 3
CPT1A	Etomoxir	Inhibition of FAO	Preclinical
CTLA-4	Ipilimumab	Checkpoint blockade; Inhibition of FAO	FDA-Approved
PD-1/PD-L1	Nivolumab, Pembrolizumab, Atezolizumab	Checkpoint blockade; Inhibition of FAO	FDA-Approved
AMPK	Metformin	Increased FAO; Inhibition of Complex I; Decreased mitochondrial ROS	FDA-Approved
mTOR	Temsirolimus, Everolimus	Inhibition of HIF-1 α translation	FDA-Approved
IDO	Epacadostat	Regulation of tryptophan metabolism; Inhibition of mTORC1	FDA-Approved
IDH1/2 mutations	Ivosidenib (AG-120), IDH305, AG-881, DS-1001b	Inhibition of 2-HG production	Phase 3
FGFR	Regorafenib, Sunitinib, TAS120	Inhibition multi-targeted kinase	Phase 2
iNOS	L-NMMA, 1400W	Inhibition of NO production	Phase 2
FOXP3	P60	suppress NF- κ B and NFAT	Preclinical

PKM2: Pyruvate kinase M2; HIF: Hypoxia inducible factor; LDH: Lactate dehydrogenase; FAO: Fatty acid oxidation; CTLA-4: Cytotoxic T-lymphocyte-associated protein 4; mTOR: Mammalian target of rapamycin; FGFR: Fibroblast growth factor receptor; FoxP3: Forkhead box P3; ROS: Reactive oxygen species.

immune cells.

Furthermore, drugs targeting tumor specific metabolic changes can also regulate the function of immune cells by altering the metabolites of the tumor. For instance, IDH1/2 inhibitors specifically reduce 2-HG production leading to destabilization of HIF-1 α in immune cells, which can cause reduction of IL-1 β secretion by macrophages.

CONCLUSION

Immunometabolism has increasingly become a component of immunology in the past decade. The current understanding suggests that a complicated metabolic network regulates the various functions of immune cells. This network can either be functionally oriented or environmentally adapted, but together, these complex interactions lead to immune microenvironment homeostasis, which affects the progression of liver cancer. However, numerous findings indicate that almost all types of immune cells present a self-contradictory function under different conditions, although the mechanisms are still unknown. In the future, more subtypes among immune cells will be defined as single cell detection systems are further developed, which may provide a key for functional heterogeneity. Therefore, liver cancer therapy that targets immunometabolism is a promising approach. Further work is urgently needed to explore the utility of targeting specific immunometabolic events in the liver cancer microenvironment for therapeutic gain.

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