

World Journal of *Gastroenterology*

World J Gastroenterol 2018 August 21; 24(31): 3469-3566



**EDITORIAL**

- 3469 Locoregional therapy response in patients with hepatocellular cancer waiting for liver transplantation: Only selection or biological effect?

Lai Q, Di Martino M, Lucatelli P, Mennini G

REVIEW

- 3472 *Helicobacter pylori*: A foodborne pathogen?

Quaglia NC, Dambrosio A

- 3488 Hepatitis B virus infection: Defective surface antigen expression and pathogenesis

Wu CC, Chen YS, Cao L, Chen XW, Lu MJ

- 3500 Immunometabolism: A novel perspective of liver cancer microenvironment and its influence on tumor progression

Zhang Q, Lou Y, Bai XL, Liang TB

MINIREVIEWS

- 3513 Osteoporosis in primary biliary cholangitis

Danford CJ, Trivedi HD, Papamichael K, Tapper EB, Bonder A

- 3521 Ubiquitin-proteasome system and oxidative stress in liver transplantation

Alva N, Panisello-Roselló A, Flores M, Roselló-Catafau J, Carbonell T

ORIGINAL ARTICLE**Basic Study**

- 3531 Stomach wall structure and vessels imaging by acoustic resolution photoacoustic microscopy

Wang C, Lu YF, Cai CM, Xiang HZ, Zheng G

- 3538 Clinical correlation of B7-H3 and B3GALT4 with the prognosis of colorectal cancer

Zhang T, Wang F, Wu JY, Qiu ZC, Wang Y, Liu F, Ge XS, Qi XW, Mao Y, Hua D

Retrospective Cohort Study

- 3547 Favorable clinical outcome of nonalcoholic liver cirrhosis patients with coronary artery disease: A population-based study

Tsai MC, Yang TW, Wang CC, Wang YT, Sung WW, Tseng MH, Lin CC

Prospective Study

- 3556 PillCamColon2 after incomplete colonoscopy - A prospective multicenter study

Baltes P, Bota M, Albert J, Philipper M, Hörster HG, Hagenmüller F, Steinbrück I, Jakobs R, Bechtler M, Hartmann D, Neuhaus H, Charton JP, Mayershofer R, Hohn H, Rösch T, Groth S, Nowak T, Wohlmuth P, Keuchel M

Contents

World Journal of Gastroenterology
Volume 24 Number 31 August 21, 2018

ABOUT COVER

Editorial board member of *World Journal of Gastroenterology*, Tamara Vorobjova, DA, PhD, Academic Research, Department of Immunology, Institute of Biomedicine and Translational Medicine, University of Tartu, Tartu 51014, Estonia

AIMS AND SCOPE

World Journal of Gastroenterology (*World J Gastroenterol*, *WJG*, print ISSN 1007-9327, online ISSN 2219-2840, DOI: 10.3748) is a peer-reviewed open access journal. *WJG* was established on October 1, 1995. It is published weekly on the 7th, 14th, 21st, and 28th each month. The *WJG* Editorial Board consists of 642 experts in gastroenterology and hepatology from 59 countries.

The primary task of *WJG* is to rapidly publish high-quality original articles, reviews, and commentaries in the fields of gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, hepatobiliary surgery, gastrointestinal oncology, gastrointestinal radiation oncology, gastrointestinal imaging, gastrointestinal interventional therapy, gastrointestinal infectious diseases, gastrointestinal pharmacology, gastrointestinal pathophysiology, gastrointestinal pathology, evidence-based medicine in gastroenterology, pancreatology, gastrointestinal laboratory medicine, gastrointestinal molecular biology, gastrointestinal immunology, gastrointestinal microbiology, gastrointestinal genetics, gastrointestinal translational medicine, gastrointestinal diagnostics, and gastrointestinal therapeutics. *WJG* is dedicated to become an influential and prestigious journal in gastroenterology and hepatology, to promote the development of above disciplines, and to improve the diagnostic and therapeutic skill and expertise of clinicians.

INDEXING/ABSTRACTING

World Journal of Gastroenterology (*WJG*) is now indexed in Current Contents[®]/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch[®]), Journal Citation Reports[®], Index Medicus, MEDLINE, PubMed, PubMed Central and Directory of Open Access Journals. The 2018 edition of Journal Citation Reports[®] cites the 2017 impact factor for *WJG* as 3.300 (5-year impact factor: 3.387), ranking *WJG* as 35th among 80 journals in gastroenterology and hepatology (quartile in category Q2).

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Electronic Editor: *Yan Huang*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Xue-Jiao Wang*
Proofing Editorial Office Director: *Ze-Mao Gong*

NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

EDITORS-IN-CHIEF
Andrzej S Tarnawski, MD, PhD, DSc (Med),
Professor of Medicine, Chief Gastroenterology, VA
Long Beach Health Care System, University of California, Irvine, CA, 5901 E. Seventh Str., Long Beach, CA 90822, United States

EDITORIAL BOARD MEMBERS
All editorial board members resources online at <http://www.wjgnet.com/1007-9327/editorialboard.htm>

EDITORIAL OFFICE
Ze-Mao Gong, Director
World Journal of Gastroenterology
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: <http://www.f6publishing.com/helpdesk>
<http://www.wjgnet.com>

PUBLISHER
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: <http://www.f6publishing.com/helpdesk>
<http://www.wjgnet.com>

PUBLICATION DATE
August 21, 2018

COPYRIGHT
© 2018 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT
All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS
Full instructions are available online at <http://www.wjgnet.com/bpg/gerinfo/204>

ONLINE SUBMISSION
<http://www.f6publishing.com>

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

Qi Zhang, Yu Lou, Xue-Li Bai, Ting-Bo Liang

Qi Zhang, Yu Lou, Xue-Li Bai, Ting-Bo Liang, Department of Hepatobiliary and Pancreatic Surgery, the Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310009, Zhejiang Province, China

Qi Zhang, Yu Lou, Xue-Li Bai, Ting-Bo Liang, Zhejiang Provincial Key Laboratory of Pancreatic Disease, Hangzhou 310009, Zhejiang Province, China

ORCID number: Qi Zhang (0000-0002-6096-0690); Yu Lou (0000-0003-2862-423X); Xue-Li Bai (0000-0001-6005-8384); Ting-Bo Liang (0000-0003-0143-3353).

Author contributions: Zhang Q and Lou Y contributed equally to this work; Liang TB and Bai XL designed the research; Zhang Q and Lou Y performed the research; Zhang Q and Lou Y wrote the paper; Liang TB and Bai XL revised the paper.

Conflict-of-interest statement: The authors declare that they have no competing interests.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Ting-Bo Liang, MD, PhD, Attending Doctor, Chief Doctor, Doctor, Full Professor, Research Fellow, Surgeon, Department of Hepatobiliary and Pancreatic Surgery, the Second Affiliated Hospital, Zhejiang University School of Medicine, No. 88 Jiefang Road, Hangzhou 310009, Zhejiang Province, China. liangtingbo@zju.edu.cn
Telephone: +86-571-87783510
Fax: +86-571-87783510

Received: April 16, 2018

Peer-review started: April 16, 2018

First decision: May 16, 2018

Revised: May 29, 2018

Accepted: June 27, 2018

Article in press: June 27, 2018

Published online: August 21, 2018

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

© **The Author(s) 2018.** Published by Baishideng Publishing Group Inc. All rights reserved.

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.

Zhang Q, Lou Y, Bai XL, Liang TB. Immunometabolism: A novel perspective of liver cancer microenvironment and its influence on tumor progression. *World J Gastroenterol* 2018; 24(31): 3500-3512 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v24/i31/3500.htm> DOI: <http://dx.doi.org/10.3748/wjg.v24.i31.3500>

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,

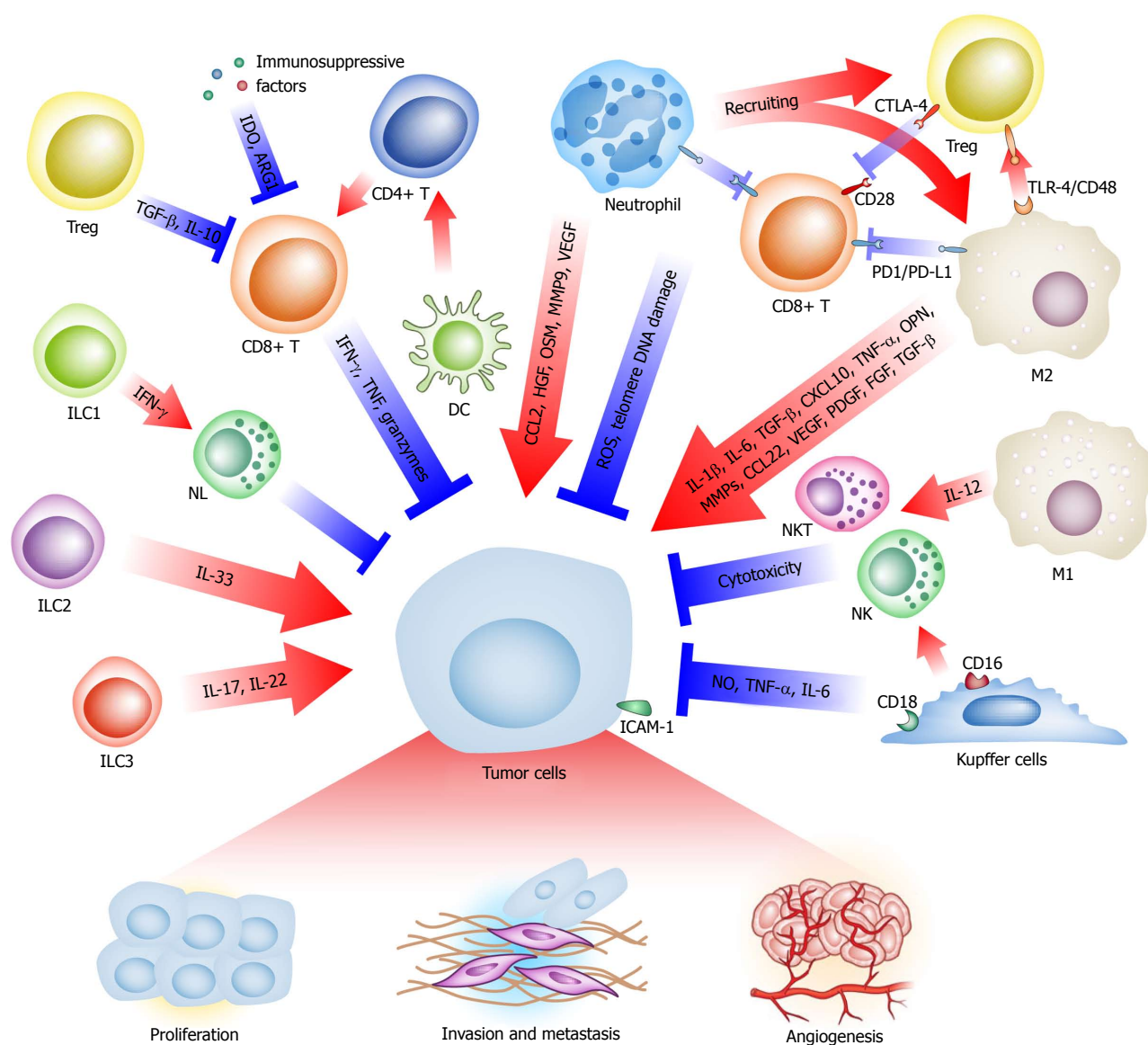


Figure 1 The immune cells in the tumor microenvironment regulate liver cancer progression. Many types of immune cells in the TME show pro- or anti-tumoral effects on the liver cancer cells by cell-specific mechanisms. Complicated crosstalk between immune cells is also common. TME: Tumor microenvironment;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

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

With their rapid growth and limited nutrition supply,

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

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

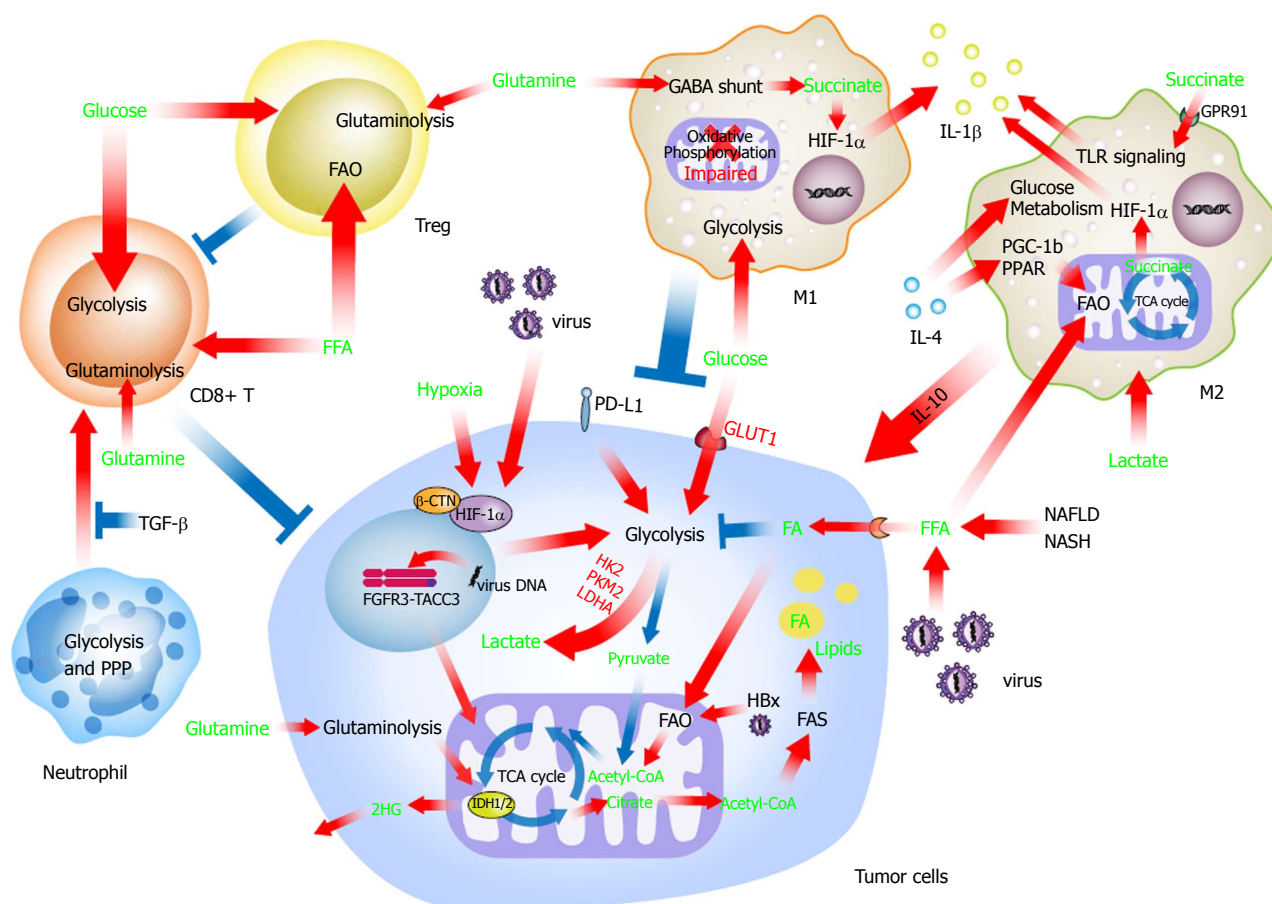


Figure 2 Metabolites in the tumor microenvironment affect the anti/pro-tumoral functions of immune cells. Energy resources including glucose, glutamine, free fatty acids, and other metabolites such as succinate largely alter the functions of macrophages, neutrophils, and T cells. These metabolically 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-tumoral 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-Ohipic, 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.

REFERENCES

- Fact sheets by Population-Globocan-IARC. IARC 2012
- Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin* 2018; **68**: 7-30 [PMID: 29313949 DOI: 10.3322/caac.21442]
- Quail DF, Joyce JA. Microenvironmental regulation of tumor progression and metastasis. *Nat Med* 2013; **19**: 1423-1437 [PMID: 24202395 DOI: 10.1038/nm.3394]
- Fang H, Declerck YA. Targeting the tumor microenvironment: from understanding pathways to effective clinical trials. *Cancer Res* 2013; **73**: 4965-4977 [PMID: 23913938 DOI: 10.1158/0008-5472.CAN-13-0661]
- Farshidfar F, Zheng S, Gingras MC, Newton Y, Shih J, Robertson AG, Hinoue T, Hoadley KA, Gibb EA, Roszik J, Covington KR, Wu CC, Shinbrot E, Stransky N, Hegde A, Yang JD, Reznik E, Sadeghi S, Pedamallu CS, Ojesina AI, Hess JM, Auman JT, Rhie SK, Bowlby R, Borad MJ; Cancer Genome Atlas Network, Zhu AX, Stuart JM, Sander C, Akbani R, Cherniack AD, Deshpande V, Mounajjed T, Foo WC, Torbenson MS, Kleiner DE, Laird PW, Wheeler DA, McRee AJ, Bathe OF, Andersen JB, Bardeesy N, Roberts LR, Kwong LN. Integrative Genomic Analysis of Cholangiocarcinoma Identifies Distinct IDH-Mutant Molecular Profiles. *Cell Rep* 2017; **18**: 2780-2794 [PMID: 28297679 DOI: 10.1016/j.celrep.2017.02.033]
- Cancer Genome Atlas Research Network. Cancer Genome Atlas Research Network. Comprehensive and Integrative Genomic Characterization of Hepatocellular Carcinoma. *Cell* 2017; **169**: 1327-1341.e23 [PMID: 28622513 DOI: 10.1016/j.cell.2017.05.046]
- Gajewski TF, Schreiber H, Fu YX. Innate and adaptive immune cells in the tumor microenvironment. *Nat Immunol* 2013; **14**: 1014-1022 [PMID: 24048123 DOI: 10.1038/ni.2703]
- Yaqoob P. Fatty acids as gatekeepers of immune cell regulation. *Trends Immunol* 2003; **24**: 639-645 [PMID: 14644137]
- Lawless SJ, Kedia-Mehta N, Walls JF, McGarrigle R, Convery O, Sinclair LV, Navarro MN, Murray J, Finlay DK. Glucose represses dendritic cell-induced T cell responses. *Nat Commun* 2017; **8**: 15620 [PMID: 28555668 DOI: 10.1038/ncomms15620]
- O'Neill LA, Kishton RJ, Rathmell J. A guide to immunometabolism for immunologists. *Nat Rev Immunol* 2016; **16**: 553-565 [PMID: 27396447 DOI: 10.1038/nri.2016.70]
- Flecken T, Schmidt N, Hild S, Gostick E, Drognitz O, Zeiser R, Schemmer P, Bruns H, Eiermann T, Price DA, Blum HE, Neumann-Haefelin C, Thimme R. Immunodominance and functional alterations of tumor-associated antigen-specific CD8+

- T-cell responses in hepatocellular carcinoma. *Hepatology* 2014; **59**: 1415-1426 [PMID: 24002931 DOI: 10.1002/hep.26731]
- 12 **Prieto J**, Melero I, Sangro B. Immunological landscape and immunotherapy of hepatocellular carcinoma. *Nat Rev Gastroenterol Hepatol* 2015; **12**: 681-700 [PMID: 26484443 DOI: 10.1038/nrgastro.2015.173]
 - 13 **Wu K**, Kryczek I, Chen L, Zou W, Welling TH. Kupffer cell suppression of CD8⁺ T cells in human hepatocellular carcinoma is mediated by B7-H1/programmed death-1 interactions. *Cancer Res* 2009; **69**: 8067-8075 [PMID: 19826049 DOI: 10.1158/0008-5472.can-09-0901]
 - 14 **Zhou SL**, Zhou ZJ, Hu ZQ, Huang XW, Wang Z, Chen EB, Fan J, Cao Y, Dai Z, Zhou J. Tumor-Associated Neutrophils Recruit Macrophages and T-Regulatory Cells to Promote Progression of Hepatocellular Carcinoma and Resistance to Sorafenib. *Gastroenterology* 2016; **150**: 1646-1658.e17 [PMID: 26924089 DOI: 10.1053/j.gastro.2016.02.040]
 - 15 **Shi JY**, Gao Q, Wang ZC, Zhou J, Wang XY, Min ZH, Shi YH, Shi GM, Ding ZB, Ke AW, Dai Z, Qiu SJ, Song K, Fan J. Margin-infiltrating CD20(+) B cells display an atypical memory phenotype and correlate with favorable prognosis in hepatocellular carcinoma. *Clin Cancer Res* 2013; **19**: 5994-6005 [PMID: 24056784 DOI: 10.1158/1078-0432.ccr-12-3497]
 - 16 **Dadi S**, Chhangawala S, Whitlock BM, Franklin RA, Luo CT, Oh SA, Toure A, Pritykin Y, Huse M, Leslie CS, Li MO. Cancer Immunosurveillance by Tissue-Resident Innate Lymphoid Cells and Innate-like T Cells. *Cell* 2016; **164**: 365-377 [PMID: 26806130 DOI: 10.1016/j.cell.2016.01.002]
 - 17 **Gonzalez-Carmona MA**, Lukacs-Kornek V, Timmerman A, Shabani S, Kornek M, Vogt A, Yildiz Y, Sievers E, Schmidt-Wolf IG, Caselmann WH, Sauerbruch T, Schmitz V. CD40ligand-expressing dendritic cells induce regression of hepatocellular carcinoma by activating innate and acquired immunity in vivo. *Hepatology* 2008; **48**: 157-168 [PMID: 18537185 DOI: 10.1002/hep.22296]
 - 18 **Schrader J**. The role of MDSCs in hepatocellular carcinoma--in vivo veritas? *J Hepatol* 2013; **59**: 921-923 [PMID: 23958935 DOI: 10.1016/j.jhep.2013.08.003]
 - 19 **Eggert T**, Wolter K, Ji J, Ma C, Yevsa T, Klotz S, Medina-Echeverez J, Longerich T, Forgues M, Reisinger F, Heikenwalder M, Wang XW, Zender L, Greten TF. Distinct Functions of Senescence-Associated Immune Responses in Liver Tumor Surveillance and Tumor Progression. *Cancer Cell* 2016; **30**: 533-547 [PMID: 27728804 DOI: 10.1016/j.ccell.2016.09.003]
 - 20 **Aono K**, Isobe K, Nakashima I, Kondo S, Miyachi M, Nimura Y. Kupffer cells cytotoxicity against hepatoma cells is related to nitric oxide. *Biochem Biophys Res Commun* 1994; **201**: 1175-1181 [PMID: 8024559 DOI: 10.1006/bbrc.1994.1829]
 - 21 **Saito H**, Kurose I, Ebinuma H, Fukumura D, Higuchi H, Atsukawa K, Tada S, Kimura H, Yonei Y, Masuda T, Miura S, Ishii H. Kupffer cell-mediated cytotoxicity against hepatoma cells occurs through production of nitric oxide and adhesion via ICAM-1/CD18. *Int Immunol* 1996; **8**: 1165-1172 [PMID: 8757962]
 - 22 **Li XY**, Wu L, Li SW, Zhou WB, Wang MY, Zuo GQ, Liu CA, Ding X. Effect of CD16a, the surface receptor of Kupffer cells, on the growth of hepatocellular carcinoma cells. *Int J Mol Med* 2016; **37**: 1465-1474 [PMID: 27082928 DOI: 10.3892/ijmm.2016.2561]
 - 23 **Rushfeldt C**, Sveinbjornsson B, Seljelid R, Smedsrod B. Early events of hepatic metastasis formation in mice: role of Kupffer and NK-cells in natural and interferon-gamma-stimulated defense. *J Surg Res* 1999; **82**: 209-215 [PMID: 10090831 DOI: 10.1006/jsre.1998.5532]
 - 24 **Seki S**, Nakashima H, Nakashima M, Kinoshita M. Antitumor immunity produced by the liver Kupffer cells, NK cells, NKT cells, and CD8 CD122 T cells. *Clin Dev Immunol* 2011; **2011**: 868345 [PMID: 22190974 DOI: 10.1155/2011/868345]
 - 25 **Ding T**, Xu J, Wang F, Shi M, Zhang Y, Li SP, Zheng L. High tumor-infiltrating macrophage density predicts poor prognosis in patients with primary hepatocellular carcinoma after resection. *Hum Pathol* 2009; **40**: 381-389 [PMID: 18992916 DOI: 10.1016/j.humpath.2008.08.011]
 - 26 **Yeung OW**, Lo CM, Ling CC, Qi X, Geng W, Li CX, Ng KT, Forbes SJ, Guan XY, Poon RT, Fan ST, Man K. Alternatively activated (M2) macrophages promote tumour growth and invasiveness in hepatocellular carcinoma. *J Hepatol* 2015; **62**: 607-616 [PMID: 25450711 DOI: 10.1016/j.jhep.2014.10.029]
 - 27 **Umamoto Y**, Okano S, Matsumoto Y, Nakagawara H, Matono R, Yoshiya S, Yamashita Y, Yoshizumi T, Ikegami T, Soejima Y, Harada M, Aishima S, Oda Y, Shirabe K, Maehara Y. Prognostic impact of programmed cell death 1 ligand 1 expression in human leukocyte antigen class I-positive hepatocellular carcinoma after curative hepatectomy. *J Gastroenterol* 2015; **50**: 65-75 [PMID: 24509608 DOI: 10.1007/s00535-014-0933-3]
 - 28 **Kuang DM**, Zhao Q, Peng C, Xu J, Zhang JP, Wu C, Zheng L. Activated monocytes in peritumoral stroma of hepatocellular carcinoma foster immune privilege and disease progression through PD-L1. *J Exp Med* 2009; **206**: 1327-1337 [PMID: 19451266 DOI: 10.1084/jem.20082173]
 - 29 **Zhou J**, Ding T, Pan W, Zhu LY, Li L, Zheng L. Increased intratumoral regulatory T cells are related to intratumoral macrophages and poor prognosis in hepatocellular carcinoma patients. *Int J Cancer* 2009; **125**: 1640-1648 [PMID: 19569243 DOI: 10.1002/ijc.24556]
 - 30 **Wu Y**, Kuang DM, Pan WD, Wan YL, Lao XM, Wang D, Li XF, Zheng L. Monocyte/macrophage-elicited natural killer cell dysfunction in hepatocellular carcinoma is mediated by CD48/2B4 interactions. *Hepatology* 2013; **57**: 1107-1116 [PMID: 23225218 DOI: 10.1002/hep.26192]
 - 31 **Yang J**, Zhang JX, Wang H, Wang GL, Hu QG, Zheng QC. Hepatocellular carcinoma and macrophage interaction induced tumor immunosuppression via Treg requires TLR4 signaling. *World J Gastroenterol* 2012; **18**: 2938-2947 [PMID: 22736917 DOI: 10.3748/wjg.v18.i23.2938]
 - 32 **Capece D**, Fischietti M, Verzella D, Gaggiano A, Ciciarelli G, Tessitore A, Zazzeroni F, Alesse E. The inflammatory microenvironment in hepatocellular carcinoma: a pivotal role for tumor-associated macrophages. *Biomed Res Int* 2013; **2013**: 187204 [PMID: 23533994 DOI: 10.1155/2013/187204]
 - 33 **Wan S**, Zhao E, Kryczek I, Vatan L, Sadovskaya A, Ludema G, Simeone DM, Zou W, Welling TH. Tumor-associated macrophages produce interleukin 6 and signal via STAT3 to promote expansion of human hepatocellular carcinoma stem cells. *Gastroenterology* 2014; **147**: 1393-1404 [PMID: 25181692 DOI: 10.1053/j.gastro.2014.08.039]
 - 34 **Wan S**, Kuo N, Kryczek I, Zou W, Welling TH. Myeloid cells in hepatocellular carcinoma. *Hepatology* 2015; **62**: 1304-1312 [PMID: 25914264 DOI: 10.1002/hep.27867]
 - 35 **Krenkel O**, Tacke F. Liver macrophages in tissue homeostasis and disease. *Nat Rev Immunol* 2017; **17**: 306-321 [PMID: 28317925 DOI: 10.1038/nri.2017.11]
 - 36 **Wilson CL**, Jurk D, Fullard N, Banks P, Page A, Luli S, Elsharkawy AM, Gieling RG, Chakraborty JB, Fox C, Richardson C, Callaghan K, Blair GE, Fox N, Lagnado A, Passos JF, Moore AJ, Smith GR, Tiniakos DG, Mann J, Oakley F, Mann DA. NFκB1 is a suppressor of neutrophil-driven hepatocellular carcinoma. *Nat Commun* 2015; **6**: 6818 [PMID: 25879839 DOI: 10.1038/ncomms7818]
 - 37 **Fridlender ZG**, Sun J, Kim S, Kapoor V, Cheng G, Ling L, Worthen GS, Albelda SM. Polarization of tumor-associated neutrophil phenotype by TGF-beta: "N1" versus "N2" TAN. *Cancer Cell* 2009; **16**: 183-194 [PMID: 19732719 DOI: 10.1016/j.ccr.2009.06.017]
 - 38 **Tsuda Y**, Fukui H, Asai A, Fukunishi S, Miyaji K, Fujiwara S, Teramura K, Fukuda A, Higuchi K. An immunosuppressive subtype of neutrophils identified in patients with hepatocellular carcinoma. *J Clin Biochem Nutr* 2012; **51**: 204-212 [PMID: 23170048 DOI: 10.3164/jcbs.12-32]
 - 39 **He G**, Zhang H, Zhou J, Wang B, Chen Y, Kong Y, Xie X, Wang X, Fei R, Wei L, Chen H, Zeng H. Peritumoral neutrophils negatively regulate adaptive immunity via the PD-L1/PD-1 signalling

- pathway in hepatocellular carcinoma. *J Exp Clin Cancer Res* 2015; **34**: 141 [PMID: 26581194 DOI: 10.1186/s13046-015-0256-0]
- 40 **Xiao WK**, Chen D, Li SQ, Fu SJ, Peng BG, Liang LJ. Prognostic significance of neutrophil-lymphocyte ratio in hepatocellular carcinoma: a meta-analysis. *BMC Cancer* 2014; **14**: 117 [PMID: 24559042 DOI: 10.1186/1471-2407-14-117]
 - 41 **da Fonseca LG**, Barroso-Sousa R, Bento Ada S, Blanco BP, Valente GL, Pfiffer TE, Hoff PM, Sabbaga J. Pre-treatment neutrophil-to-lymphocyte ratio affects survival in patients with advanced hepatocellular carcinoma treated with sorafenib. *Med Oncol* 2014; **31**: 264 [PMID: 25273866 DOI: 10.1007/s12032-014-0264-5]
 - 42 **Motomura T**, Shirabe K, Mano Y, Muto J, Toshima T, Umemoto Y, Fukuhara T, Uchiyama H, Ikegami T, Yoshizumi T, Soejima Y, Maehara Y. Neutrophil-lymphocyte ratio reflects hepatocellular carcinoma recurrence after liver transplantation via inflammatory microenvironment. *J Hepatol* 2013; **58**: 58-64 [PMID: 22925812 DOI: 10.1016/j.jhep.2012.08.017]
 - 43 **Imai Y**, Kubota Y, Yamamoto S, Tsuji K, Shimatani M, Shibatani N, Takamido S, Matsushita M, Okazaki K. Neutrophils enhance invasion activity of human cholangiocellular carcinoma and hepatocellular carcinoma cells: an in vitro study. *J Gastroenterol Hepatol* 2005; **20**: 287-293 [PMID: 15683434 DOI: 10.1111/j.1440-1746.2004.03575.x]
 - 44 **He M**, Peng A, Huang XZ, Shi DC, Wang JC, Zhao Q, Lin H, Kuang DM, Ke PF, Lao XM. Peritumoral stromal neutrophils are essential for c-Met-elicited metastasis in human hepatocellular carcinoma. *Oncotarget* 2016; **5**: e1219828 [PMID: 27853643 DOI: 10.1080/2162402x.2016.1219828]
 - 45 **Li XF**, Chen DP, Ouyang FZ, Chen MM, Wu Y, Kuang DM, Zheng L. Increased autophagy sustains the survival and protumorigenic effects of neutrophils in human hepatocellular carcinoma. *J Hepatol* 2015; **62**: 131-139 [PMID: 25152203 DOI: 10.1016/j.jhep.2014.08.023]
 - 46 **Kuang DM**, Zhao Q, Wu Y, Peng C, Wang J, Xu Z, Yin XY, Zheng L. Peritumoral neutrophils link inflammatory response to disease progression by fostering angiogenesis in hepatocellular carcinoma. *J Hepatol* 2011; **54**: 948-955 [PMID: 21145847 DOI: 10.1016/j.jhep.2010.08.041]
 - 47 **Xu R**, Huang H, Zhang Z, Wang FS. The role of neutrophils in the development of liver diseases. *Cell Mol Immunol* 2014; **11**: 224-231 [PMID: 24633014 DOI: 10.1038/cmi.2014.2]
 - 48 **Guo CL**, Yang HC, Yang XH, Cheng W, Dong TX, Zhu WJ, Xu Z, Zhao L. Associations between infiltrating lymphocyte subsets and hepatocellular carcinoma. *Asian Pac J Cancer Prev* 2012; **13**: 5909-5913 [PMID: 23317279]
 - 49 **Fu J**, Xu D, Liu Z, Shi M, Zhao P, Fu B, Zhang Z, Yang H, Zhang H, Zhou C, Yao J, Jin L, Wang H, Yang Y, Fu YX, Wang FS. Increased regulatory T cells correlate with CD8 T-cell impairment and poor survival in hepatocellular carcinoma patients. *Gastroenterology* 2007; **132**: 2328-2339 [PMID: 17570208 DOI: 10.1053/j.gastro.2007.03.102]
 - 50 **Kalathil S**, Lugade AA, Miller A, Iyer R, Thanavala Y. Higher frequencies of GARP(+)CTLA-4(+)Foxp3(+) T regulatory cells and myeloid-derived suppressor cells in hepatocellular carcinoma patients are associated with impaired T-cell functionality. *Cancer Res* 2013; **73**: 2435-2444 [PMID: 23423978 DOI: 10.1158/0008-5472.can-12-3381]
 - 51 **Garnelo M**, Tan A, Her Z, Yeong J, Lim CJ, Chen J, Lim KH, Weber A, Chow P, Chung A, Ooi LL, Toh HC, Heikenwalder M, Ng IO, Nardin A, Chen Q, Abastado JP, Chew V. Interaction between tumour-infiltrating B cells and T cells controls the progression of hepatocellular carcinoma. *Gut* 2017; **66**: 342-351 [PMID: 26669617 DOI: 10.1136/gutjnl-2015-310814]
 - 52 **Ringelhan M**, Pfister D, O'Connor T, Pikarsky E, Heikenwalder M. The immunology of hepatocellular carcinoma. *Nature Immunology* 2018; **19**: 222-232 [DOI: 10.1038/s41590-018-0044-z]
 - 53 **Yang S**, Tian Z, Wu Y, van Velkinburgh JC, Ni B. Pivotal roles of ILCs in hepatic diseases. *Int Rev Immunol* 2015; **34**: 509-522 [PMID: 25730441 DOI: 10.3109/08830185.2015.1008631]
 - 54 **Artis D**, Spits H. The biology of innate lymphoid cells. *Nature* 2015; **517**: 293-301 [PMID: 25592534 DOI: 10.1038/nature14189]
 - 55 **Abe H**, Kimura A, Tsuruta S, Fukaya T, Sakaguchi R, Morita R, Sekiya T, Shichita T, Chayama K, Fujii-Kuriyama Y, Yoshimura A. Aryl hydrocarbon receptor plays protective roles in ConA-induced hepatic injury by both suppressing IFN- γ expression and inducing IL-22. *Int Immunol* 2014; **26**: 129-137 [PMID: 24150244 DOI: 10.1093/intimm/dxt049]
 - 56 **Kirchberger S**, Royston DJ, Boulard O, Thornton E, Franchini F, Szabady RL, Harrison O, Powrie F. Innate lymphoid cells sustain colon cancer through production of interleukin-22 in a mouse model. *J Exp Med* 2013; **210**: 917-931 [PMID: 23589566 DOI: 10.1084/jem.20122308]
 - 57 **Zhang P**, Liu XK, Chu Z, Ye JC, Li KL, Zhuang WL, Yang DJ, Jiang YF. Detection of interleukin-33 in serum and carcinoma tissue from patients with hepatocellular carcinoma and its clinical implications. *J Int Med Res* 2012; **40**: 1654-1661 [PMID: 23206447 DOI: 10.1177/030006051204000504]
 - 58 **Li J**, Razumilava N, Gores GJ, Walters S, Mizuochi T, Mourya R, Bessho K, Wang YH, Glaser SS, Shivakumar P, Bezerra JA. Biliary repair and carcinogenesis are mediated by IL-33-dependent cholangiocyte proliferation. *J Clin Invest* 2014; **124**: 3241-3251 [PMID: 24892809 DOI: 10.1172/jci73742]
 - 59 **Jovanovic IP**, Pejnovic NN, Radosavljevic GD, Pantic JM, Milovanovic MZ, Arsenijevic NN, Lukic ML. Interleukin-33/ST2 axis promotes breast cancer growth and metastases by facilitating intratumoral accumulation of immunosuppressive and innate lymphoid cells. *Int J Cancer* 2014; **134**: 1669-1682 [PMID: 24105680 DOI: 10.1002/ijc.28481]
 - 60 **McHedlidze T**, Waldner M, Zopf S, Walker J, Rankin AL, Schuchmann M, Voehringer D, McKenzie AN, Neurath MF, Pflanz S, Wirtz S. Interleukin-33-dependent innate lymphoid cells mediate hepatic fibrosis. *Immunity* 2013; **39**: 357-371 [PMID: 23954132 DOI: 10.1016/j.immuni.2013.07.018]
 - 61 **Hanahan D**, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011; **144**: 646-674 [PMID: 21376230 DOI: 10.1016/j.cell.2011.02.013]
 - 62 **Kettner NM**, Voicu H, Finegold MJ, Coarfa C, Sreekumar A, Putluri N, Katchy CA, Lee C, Moore DD, Fu L. Circadian Homeostasis of Liver Metabolism Suppresses Hepatocarcinogenesis. *Cancer Cell* 2016; **30**: 909-924 [PMID: 27889186 DOI: 10.1016/j.ccell.2016.10.007]
 - 63 **Huang Q**, Tan Y, Yin P, Ye G, Gao P, Lu X, Wang H, Xu G. Metabolic characterization of hepatocellular carcinoma using nontargeted tissue metabolomics. *Cancer Res* 2013; **73**: 4992-5002 [PMID: 23824744 DOI: 10.1158/0008-5472.CAN-13-0308]
 - 64 **Gingold JA**, Zhu D, Lee DF, Kaseb A, Chen J. Genomic Profiling and Metabolic Homeostasis in Primary Liver Cancers. *Trends Mol Med* 2018; **24**: 395-411 [PMID: 29530485 DOI: 10.1016/j.molmed.2018.02.006]
 - 65 **Ngo H**, Tortorella SM, Ververis K, Karagiannis TC. The Warburg effect: molecular aspects and therapeutic possibilities. *Mol Biol Rep* 2015; **42**: 825-834 [PMID: 25253100 DOI: 10.1007/s11033-014-3764-7]
 - 66 **Jones RG**, Thompson CB. Tumor suppressors and cell metabolism: a recipe for cancer growth. *Genes Dev* 2009; **23**: 537-548 [PMID: 19270154 DOI: 10.1101/gad.1756509]
 - 67 **Shang RZ**, Qu SB, Wang DS. Reprogramming of glucose metabolism in hepatocellular carcinoma: Progress and prospects. *World J Gastroenterol* 2016; **22**: 9933-9943 [PMID: 28018100 DOI: 10.3748/wjg.v22.i45.9933]
 - 68 **Zhang Q**, Bai X, Chen W, Ma T, Hu Q, Liang C, Xie S, Chen C, Hu L, Xu S, Liang T. Wnt/ β -catenin signaling enhances hypoxia-induced epithelial-mesenchymal transition in hepatocellular carcinoma via crosstalk with hif-1 α signaling. *Carcinogenesis* 2013; **34**: 962-973 [PMID: 23358852 DOI: 10.1093/carcin/bgt027]
 - 69 **Kitamura K**, Hatano E, Higashi T, Narita M, Seo S, Nakamoto Y, Yamanaka K, Nagata H, Taura K, Yasuchika K, Nitta T, Uemoto S. Proliferative activity in hepatocellular carcinoma is closely correlated with glucose metabolism but not angiogenesis.

- J Hepatol* 2011; **55**: 846-857 [PMID: 21334407 DOI: 10.1016/j.jhep.2011.01.038]
- 70 **Jia YY**, Zhao JY, Li BL, Gao K, Song Y, Liu MY, Yang XJ, Xue Y, Wen AD, Shi L. miR-592/WSB1/HIF-1 α axis inhibits glycolytic metabolism to decrease hepatocellular carcinoma growth. *Oncotarget* 2016; **7**: 35257-35269 [PMID: 27153552 DOI: 10.18632/oncotarget.9135]
 - 71 **Jiang J**, Nilsson-Ehle P, Xu N. Influence of liver cancer on lipid and lipoprotein metabolism. *Lipids Health Dis* 2006; **5**: 4 [PMID: 16515689 DOI: 10.1186/1476-511x-5-4]
 - 72 **Budhu A**, Roessler S, Zhao X, Yu Z, Forgues M, Ji J, Karoly E, Qin LX, Ye QH, Jia HL, Fan J, Sun HC, Tang ZY, Wang XW. Integrated metabolite and gene expression profiles identify lipid biomarkers associated with progression of hepatocellular carcinoma and patient outcomes. *Gastroenterology* 2013; **144**: 1066-1075.e1 [PMID: 23376425 DOI: 10.1053/j.gastro.2013.01.054]
 - 73 **Yang H**, Ye D, Guan KL, Xiong Y. IDH1 and IDH2 mutations in tumorigenesis: mechanistic insights and clinical perspectives. *Clin Cancer Res* 2012; **18**: 5562-5571 [PMID: 23071358 DOI: 10.1158/1078-0432.CCR-12-1773]
 - 74 **Turkalp Z**, Karamchandani J, Das S. IDH mutation in glioma: new insights and promises for the future. *JAMA Neurol* 2014; **71**: 1319-1325 [PMID: 25155243 DOI: 10.1001/jamaneurol.2014.1205]
 - 75 **Borger DR**, Goyal L, Yau T, Poon RT, Ancukiewicz M, Deshpande V, Christiani DC, Liebman HM, Yang H, Kim H, Yen K, Faris JE, Iafrate AJ, Kwak EL, Clark JW, Allen JN, Blaszkowsky LS, Murphy JE, Saha SK, Hong TS, Wo JY, Ferrone CR, Tanabe KK, Bardeesy N, Straley KS, Agresta S, Schenkein DP, Elisen LW, Ryan DP, Zhu AX. Circulating oncometabolite 2-hydroxyglutarate is a potential surrogate biomarker in patients with isocitrate dehydrogenase-mutant intrahepatic cholangiocarcinoma. *Clin Cancer Res* 2014; **20**: 1884-1890 [PMID: 24478380 DOI: 10.1158/1078-0432.CCR-13-2649]
 - 76 **Fathi AT**, Nahed BV, Wander SA, Iafrate AJ, Borger DR, Hu R, Thabet A, Cahill DP, Perry AM, Joseph CP, Muzikansky A, Chi AS. Elevation of Urinary 2-Hydroxyglutarate in IDH-Mutant Glioma. *Oncologist* 2016; **21**: 214-219 [PMID: 26834160 DOI: 10.1634/theoncologist.2015-0342]
 - 77 **Chen JY**, Lai YS, Tsai HJ, Kuo CC, Yen BL, Yeh SP, Sun HS, Hung WC. The oncometabolite R-2-hydroxyglutarate activates NF- κ B-dependent tumor-promoting stromal niche for acute myeloid leukemia cells. *Sci Rep* 2016; **6**: 32428 [PMID: 27577048 DOI: 10.1038/srep32428]
 - 78 **Zhang C**, Moore LM, Li X, Yung WK, Zhang W. IDH1/2 mutations target a key hallmark of cancer by deregulating cellular metabolism in glioma. *Neuro Oncol* 2013; **15**: 1114-1126 [PMID: 23877318 DOI: 10.1093/neuonc/not087]
 - 79 **Izquierdo-Garcia JL**, Viswanath P, Eriksson P, Cai L, Radoul M, Chaumeil MM, Blough M, Luchman HA, Weiss S, Cairncross JG, Phillips JJ, Pieper RO, Ronen SM. IDH1 Mutation Induces Reprogramming of Pyruvate Metabolism. *Cancer Res* 2015; **75**: 2999-3009 [PMID: 26045167 DOI: 10.1158/0008-5472.can-15-0840]
 - 80 **Bogdanovic E**. IDH1, lipid metabolism and cancer: Shedding new light on old ideas. *Biochim Biophys Acta* 2015; **1850**: 1781-1785 [PMID: 25960387 DOI: 10.1016/j.bbagen.2015.04.014]
 - 81 **Arai Y**, Totoki Y, Hosoda F, Shiota T, Hama N, Nakamura H, Ojima H, Furuta K, Shimada K, Okusaka T, Kosuge T, Shibata T. Fibroblast growth factor receptor 2 tyrosine kinase fusions define a unique molecular subtype of cholangiocarcinoma. *Hepatology* 2014; **59**: 1427-1434 [PMID: 24122810 DOI: 10.1002/hep.26890]
 - 82 **Cheng AL**, Shen YC, Zhu AX. Targeting fibroblast growth factor receptor signaling in hepatocellular carcinoma. *Oncology* 2011; **81**: 372-380 [PMID: 22269894 DOI: 10.1159/000335472]
 - 83 **Churi CR**, Shroff R, Wang Y, Rashid A, Kang HC, Weatherly J, Zuo M, Zinner R, Hong D, Meric-Bernstam F, Janku F, Crane CH, Mishra L, Vauthey JN, Wolff RA, Mills G, Javle M. Mutation profiling in cholangiocarcinoma: prognostic and therapeutic implications. *PLoS One* 2014; **9**: e115383 [PMID: 25536104 DOI: 10.1371/journal.pone.0115383]
 - 84 **Sia D**, Tovar V, Moeini A, Llovet JM. Intrahepatic cholangiocarcinoma: pathogenesis and rationale for molecular therapies. *Oncogene* 2013; **32**: 4861-4870 [PMID: 23318457 DOI: 10.1038/onc.2012.617]
 - 85 **Wu YM**, Su F, Kalyana-Sundaram S, Khazanov N, Ateeq B, Cao X, Lonigro RJ, Vats P, Wang R, Lin SF, Cheng AJ, Kunju LP, Siddiqui J, Tomlins SA, Wyngaard P, Sadis S, Roychowdhury S, Hussain MH, Feng FY, Zalupski MM, Talpaz M, Pienta KJ, Rhodes DR, Robinson DR, Chinnaiyan AM. Identification of targetable FGFR gene fusions in diverse cancers. *Cancer Discov* 2013; **3**: 636-647 [PMID: 23558953 DOI: 10.1158/2159-8290.cd-13-0050]
 - 86 **Frattini V**, Pagnotta SM, Tala, Fan JJ, Russo MV, Lee SB, Garofano L, Zhang J, Shi P, Lewis G, Sanson H, Frederick V, Castano AM, Cerulo L, Rolland DCM, Mall R, Mokhtari K, Elenitoba-Johnson KSJ, Sanson M, Huang X, Ceccarelli M, Lasorella A, Iavarone A. A metabolic function of FGFR3-TACC3 gene fusions in cancer. *Nature* 2018; **553**: 222-227 [PMID: 29323298 DOI: 10.1038/nature25171]
 - 87 **Chiang CH**, Huang KC. Association between metabolic factors and chronic hepatitis B virus infection. *World J Gastroenterol* 2014; **20**: 7213-7216 [PMID: 24966591 DOI: 10.3748/wjg.v20.i23.7213]
 - 88 **Schoeman JC**, Hou J, Harms AC, Vreeken RJ, Berger R, Hankemeier T, Boonstra A. Metabolic characterization of the natural progression of chronic hepatitis B. *Genome Med* 2016; **8**: 64 [PMID: 27286979 DOI: 10.1186/s13073-016-0318-8]
 - 89 **Agani F**, Jiang BH. Oxygen-independent regulation of HIF-1: novel involvement of PI3K/AKT/mTOR pathway in cancer. *Curr Cancer Drug Targets* 2013; **13**: 245-251 [PMID: 23297826]
 - 90 **Kasuno K**, Takabuchi S, Fukuda K, Kizaka-Kondoh S, Yodoi J, Adachi T, Semenza GL, Hirota K. Nitric oxide induces hypoxia-inducible factor 1 activation that is dependent on MAPK and phosphatidylinositol 3-kinase signaling. *J Biol Chem* 2004; **279**: 2550-2558 [PMID: 14600153 DOI: 10.1074/jbc.M308197200]
 - 91 **Tanaka H**, Yamamoto M, Hashimoto N, Miyakoshi M, Tamakawa S, Yoshie M, Tokusashi Y, Yokoyama K, Yaginuma Y, Ogawa K. Hypoxia-independent overexpression of hypoxia-inducible factor 1 α as an early change in mouse hepatocarcinogenesis. *Cancer Res* 2006; **66**: 11263-11270 [PMID: 17145871 DOI: 10.1158/0008-5472.can-06-1699]
 - 92 **Xia L**, Mo P, Huang W, Zhang L, Wang Y, Zhu H, Tian D, Liu J, Chen Z, Zhang Y, Chen Z, Hu H, Fan D, Nie Y, Wu K. The TNF- α /ROS/HIF-1-induced upregulation of FoxM1 expression promotes HCC proliferation and resistance to apoptosis. *Carcinogenesis* 2012; **33**: 2250-2259 [PMID: 22831955 DOI: 10.1093/carcin/bgs249]
 - 93 **Wang MD**, Wu H, Huang S, Zhang HL, Qin CJ, Zhao LH, Fu GB, Zhou X, Wang XM, Tang L, Wen W, Yang W, Tang SH, Cao D, Guo LN, Zeng M, Wu MC, Yan HX, Wang HY. HBx regulates fatty acid oxidation to promote hepatocellular carcinoma survival during metabolic stress. *Oncotarget* 2016; **7**: 6711-6726 [PMID: 26744319 DOI: 10.18632/oncotarget.6817]
 - 94 **Kim K**, Kim KH, Kim HH, Cheong J. Hepatitis B virus X protein induces lipogenic transcription factor SREBP1 and fatty acid synthase through the activation of nuclear receptor LXR α . *Biochem J* 2008; **416**: 219-230 [PMID: 18782084 DOI: 10.1042/bj20081336]
 - 95 **Kim SY**, Kim JK, Kim HJ, Ahn JK. Hepatitis B virus X protein sensitizes UV-induced apoptosis by transcriptional transactivation of Fas ligand gene expression. *IUBMB Life* 2005; **57**: 651-658 [PMID: 16203685 DOI: 10.1080/15216540500239697]
 - 96 **Dai CY**, Yeh ML, Huang CF, Hou CH, Hsieh MY, Huang JF, Lin IL, Lin ZY, Chen SC, Wang LY, Chuang WL, Yu ML, Tung HD. Chronic hepatitis C infection is associated with insulin resistance and lipid profiles. *J Gastroenterol Hepatol* 2015; **30**: 879-884 [PMID: 23808794 DOI: 10.1111/jgh.12313]
 - 97 **Kawaguchi Y**, Mizuta T. Interaction between hepatitis C virus and metabolic factors. *World J Gastroenterol* 2014; **20**: 2888-2901 [PMID: 24659880 DOI: 10.3748/wjg.v20.i11.2888]

- 98 **Bernsmeier C**, Calabrese D, Heim MH, Duong HT. Hepatitis C virus dysregulates glucose homeostasis by a dual mechanism involving induction of PGC1 α and dephosphorylation of FoxO1. *J Viral Hepat* 2014; **21**: 9-18 [PMID: 24329853 DOI: 10.1111/jvh.12208]
- 99 **Lee S**, Mardinoglu A, Zhang C, Lee D, Nielsen J. Dysregulated signaling hubs of liver lipid metabolism reveal hepatocellular carcinoma pathogenesis. *Nucleic Acids Res* 2016; **44**: 5529-5539 [PMID: 27216817 DOI: 10.1093/nar/gkw462]
- 100 **Sanyal AJ**, Campbell-Sargent C, Mirshahi F, Rizzo WB, Contos MJ, Sterling RK, Luketic VA, Shiffman ML, Clore JN. Nonalcoholic steatohepatitis: association of insulin resistance and mitochondrial abnormalities. *Gastroenterology* 2001; **120**: 1183-1192 [PMID: 11266382 DOI: 10.1053/gast.2001.23256]
- 101 **Satapati S**, Kucejova B, Duarte JA, Fletcher JA, Reynolds L, Sunny NE, He T, Nair LA, Livingston KA, Fu X, Merritt ME, Sherry AD, Malloy CR, Shelton JM, Lambert J, Parks EJ, Corbin I, Magnuson MA, Browning JD, Burgess SC. Mitochondrial metabolism mediates oxidative stress and inflammation in fatty liver. *J Clin Invest* 2015; **125**: 4447-4462 [PMID: 26571396 DOI: 10.1172/JCI82204]
- 102 **Nassir F**, Ibdah JA. Role of mitochondria in nonalcoholic fatty liver disease. *Int J Mol Sci* 2014; **15**: 8713-8742 [PMID: 24837835 DOI: 10.3390/ijms15058713]
- 103 **Fromenty B**, Robin MA, Igoudjil A, Mansouri A, Pessayre D. The ins and outs of mitochondrial dysfunction in NASH. *Diabetes Metab* 2004; **30**: 121-138 [PMID: 15223984]
- 104 **Fujisawa K**, Takami T, Matsumoto T, Yamamoto N, Sakaida I. Profiling of the circadian metabolome in thioacetamide-induced liver cirrhosis in mice. *Hepatol Commun* 2017; **1**: 704-718 [PMID: 29404487 DOI: 10.1002/hep4.1075]
- 105 **Nishikawa T**, Bellance N, Damm A, Bing H, Zhu Z, Handa K, Yovchev MI, Sehgal V, Moss TJ, Oertel M, Ram PT, Pipinos II, Soto-Gutierrez A, Fox IJ, Nagrath D. A switch in the source of ATP production and a loss in capacity to perform glycolysis are hallmarks of hepatocyte failure in advance liver disease. *J Hepatol* 2014; **60**: 1203-1211 [PMID: 24583248 DOI: 10.1016/j.jhep.2014.02.014]
- 106 **Andrejeva G**, Rathmell JC. Similarities and Distinctions of Cancer and Immune Metabolism in Inflammation and Tumors. *Cell Metab* 2017; **26**: 49-70 [PMID: 28683294 DOI: 10.1016/j.cmet.2017.06.004]
- 107 **Haschemi A**, Kosma P, Gille L, Evans CR, Burant CF, Starkl P, Knapp B, Haas R, Schmid JA, Jandl C, Amir S, Lubec G, Park J, Esterbauer H, Bilban M, Brizuela L, Pospisilik JA, Otterbein LE, Wagner O. The sedoheptulose kinase CARKL directs macrophage polarization through control of glucose metabolism. *Cell Metab* 2012; **15**: 813-826 [PMID: 22682222 DOI: 10.1016/j.cmet.2012.04.023]
- 108 **Huang SC**, Everts B, Ivanova Y, O'Sullivan D, Nascimento M, Smith AM, Beatty W, Love-Gregory L, Lam WY, O'Neill CM, Yan C, Du H, Abumrad NA, Urban JF Jr, Artyomov MN, Pearce EL, Pearce EJ. Cell-intrinsic lysosomal lipolysis is essential for alternative activation of macrophages. *Nat Immunol* 2014; **15**: 846-855 [PMID: 25086775 DOI: 10.1038/ni.2956]
- 109 **Namgaladze D**, Brüne B. Fatty acid oxidation is dispensable for human macrophage IL-4-induced polarization. *Biochim Biophys Acta* 2014; **1841**: 1329-1335 [PMID: 24960101 DOI: 10.1016/j.bbalip.2014.06.007]
- 110 **Nomura M**, Liu J, Rovira II, Gonzalez-Hurtado E, Lee J, Wolfgang MJ, Finkel T. Fatty acid oxidation in macrophage polarization. *Nat Immunol* 2016; **17**: 216-217 [PMID: 26882249 DOI: 10.1038/ni.3366]
- 111 **Zhang Q**, Wang HR, Mao CY, Sun M, Dominah G, Chen L, Zhuang Z. Fatty acid oxidation contributes to IL-1 β secretion in M2 macrophages and promotes macrophage-mediated tumor cell migration. *Mol Metab* 2018; **94**: 27-35 [DOI: 10.1016/j.molimm.2017.12.011]
- 112 **Vats D**, Mukundan L, Odegaard JI, Zhang L, Smith KL, Morel CR, Wagner RA, Greaves DR, Murray PJ, Chawla A. Oxidative metabolism and PGC-1 β attenuate macrophage-mediated inflammation. *Cell Metab* 2006; **4**: 13-24 [PMID: 16814729 DOI: 10.1016/j.cmet.2006.05.011]
- 113 **Biswas SK**. Metabolic Reprogramming of Immune Cells in Cancer Progression. *Immunity* 2015; **43**: 435-449 [PMID: 26377897 DOI: 10.1016/j.immuni.2015.09.001]
- 114 **Covarrubias AJ**, Aksoylar HI, Yu J, Snyder NW, Worth AJ, Iyer SS, Wang J, Ben-Sahra I, Byles V, Polynne-Stapornkul T, Espinosa EC, Lamming D, Manning BD, Zhang Y, Blair IA, Horng T. Akt-mTORC1 signaling regulates Acly to integrate metabolic input to control of macrophage activation. *Elife* 2016; **5** [PMID: 26894960 DOI: 10.7554/eLife.11612]
- 115 **Lim JE**, Chung E, Son Y. A neuropeptide, Substance-P, directly induces tissue-repairing M2 like macrophages by activating the PI3K/Akt/mTOR pathway even in the presence of IFN γ . *Sci Rep* 2017; **7**: 9417 [PMID: 28842601 DOI: 10.1038/s41598-017-09639-7]
- 116 **Zhou L**, Wang Q, Yin P, Xing W, Wu Z, Chen S, Lu X, Zhang Y, Lin X, Xu G. Serum metabolomics reveals the deregulation of fatty acids metabolism in hepatocellular carcinoma and chronic liver diseases. *Anal Bioanal Chem* 2012; **403**: 203-213 [PMID: 22349331 DOI: 10.1007/s00216-012-5782-4]
- 117 **Nath A**, Li I, Roberts LR, Chan C. Elevated free fatty acid uptake via CD36 promotes epithelial-mesenchymal transition in hepatocellular carcinoma. *Sci Rep* 2015; **5**: 14752 [PMID: 26424075 DOI: 10.1038/srep14752]
- 118 **Feingold KR**, Shigenaga JK, Kazemi MR, McDonald CM, Patzek SM, Cross AS, Moser A, Grunfeld C. Mechanisms of triglyceride accumulation in activated macrophages. *J Leukoc Biol* 2012; **92**: 829-839 [PMID: 22753953 DOI: 10.1189/jlb.1111537]
- 119 **Colegio OR**, Chu NQ, Szabo AL, Chu T, Rhebergen AM, Jairam V, Cyrus N, Brokowski CE, Eisenbarth SC, Phillips GM, Cline GW, Phillips AJ, Medzhitov R. Functional polarization of tumour-associated macrophages by tumour-derived lactic acid. *Nature* 2014; **513**: 559-563 [PMID: 25043024 DOI: 10.1038/nature13490]
- 120 **Ruan GX**, Kazlauskas A. Lactate engages receptor tyrosine kinases Axl, Tie2, and vascular endothelial growth factor receptor 2 to activate phosphoinositide 3-kinase/Akt and promote angiogenesis. *J Biol Chem* 2013; **288**: 21161-21172 [PMID: 23754286 DOI: 10.1074/jbc.M113.474619]
- 121 **Ohashi T**, Aoki M, Tomita H, Akazawa T, Sato K, Kuze B, Mizuta K, Hara A, Nagaoka H, Inoue N, Ito Y. M2-like macrophage polarization in high lactic acid-producing head and neck cancer. *Cancer Sci* 2017; **108**: 1128-1134 [PMID: 28370718 DOI: 10.1111/cas.13244]
- 122 **Spadaro O**, Camell CD, Bosurgi L, Nguyen KY, Youm YH, Rothlin CV, Dixit VD. IGF1 Shapes Macrophage Activation in Response to Immunometabolic Challenge. *Cell Rep* 2017; **19**: 225-234 [PMID: 28402847 DOI: 10.1016/j.celrep.2017.03.046]
- 123 **Pearce EL**, Pearce EJ. Metabolic pathways in immune cell activation and quiescence. *Immunity* 2013; **38**: 633-643 [PMID: 23601682 DOI: 10.1016/j.immuni.2013.04.005]
- 124 **Palsson-McDermott EM**, Curtis AM, Goel G, Lauterbach MA, Sheedy FJ, Gleeson LE, van den Bosch MW, Quinn SR, Domingo-Fernandez R, Johnston DG, Jiang JK, Israelsen WJ, Keane J, Thomas C, Clish C, Vander Heiden M, Xavier RJ, O'Neill LA. Pyruvate kinase M2 regulates Hif-1 α activity and IL-1 β induction and is a critical determinant of the warburg effect in LPS-activated macrophages. *Cell Metab* 2015; **21**: 65-80 [PMID: 25565206 DOI: 10.1016/j.cmet.2014.12.005]
- 125 **Moon JS**, Nakahira K, Chung KP, DeNicola GM, Koo MJ, Pabón MA, Rooney KT, Yoon JH, Ryter SW, Stout-Delgado H, Choi AM. NOX4-dependent fatty acid oxidation promotes NLRP3 inflammasome activation in macrophages. *Nat Med* 2016; **22**: 1002-1012 [PMID: 27455510 DOI: 10.1038/nm.4153]
- 126 **Moon JS**, Hisata S, Park MA, DeNicola GM, Ryter SW, Nakahira K, Choi AMK. mTORC1-Induced HK1-Dependent Glycolysis Regulates NLRP3 Inflammasome Activation. *Cell Rep* 2015; **12**: 102-115 [PMID: 26119735 DOI: 10.1016/j.celrep.2015.05.046]
- 127 **Littlewood-Evans A**, Sarret S, Apfel V, Loesle P, Dawson J, Zhang

- J, Muller A, Tigani B, Kneuer R, Patel S, Valeaux S, Gommermann N, Rubic-Schneider T, Junt T, Carballido JM. GPR91 senses extracellular succinate released from inflammatory macrophages and exacerbates rheumatoid arthritis. *J Exp Med* 2016; **213**: 1655-1662 [PMID: 27481132 DOI: 10.1084/jem.20160061]
- 128 **Mills EL**, Kelly B, Logan A, Costa ASH, Varma M, Bryant CE, Tourlomousis P, Däbritz JHM, Gottlieb E, Latorre I, Corr SC, McManus G, Ryan D, Jacobs HT, Szibor M, Xavier RJ, Braun T, Frezza C, Murphy MP, O'Neill LA. Succinate Dehydrogenase Supports Metabolic Repurposing of Mitochondria to Drive Inflammatory Macrophages. *Cell* 2016; **167**: 457-470.e13 [PMID: 27667687 DOI: 10.1016/j.cell.2016.08.064]
- 129 **Tannahill GM**, Curtis AM, Adamik J, Palsson-McDermott EM, McGettrick AF, Goel G, Frezza C, Bernard NJ, Kelly B, Foley NH, Zheng L, Gardet A, Tong Z, Jany SS, Corr SC, Haneklaus M, Caffrey BE, Pierce K, Walmsley S, Beasley FC, Cummins E, Nizet V, Whyte M, Taylor CT, Lin H, Masters SL, Gottlieb E, Kelly VP, Clish C, Auron PE, Xavier RJ, O'Neill LA. Succinate is an inflammatory signal that induces IL-1 β through HIF-1 α . *Nature* 2013; **496**: 238-242 [PMID: 23535595 DOI: 10.1038/nature11986]
- 130 **Azevedo EP**, Rochael NC, Guimarães-Costa AB, de Souza-Vieira TS, Ganilho J, Saraiva EM, Palhano FL, Foguel D. A Metabolic Shift toward Pentose Phosphate Pathway Is Necessary for Amyloid Fibril- and Phorbol 12-Myristate 13-Acetate-induced Neutrophil Extracellular Trap (NET) Formation. *J Biol Chem* 2015; **290**: 22174-22183 [PMID: 26198639 DOI: 10.1074/jbc.M115.640094]
- 131 **Siska PJ**, Rathmell JC. T cell metabolic fitness in antitumor immunity. *Trends Immunol* 2015; **36**: 257-264 [PMID: 25773310 DOI: 10.1016/j.it.2015.02.007]
- 132 **Chang CH**, Curtis JD, Maggi LB Jr, Faubert B, Villarino AV, O'Sullivan D, Huang SC, van der Windt GJ, Blagih J, Qiu J, Weber JD, Pearce EJ, Jones RG, Pearce EL. Posttranscriptional control of T cell effector function by aerobic glycolysis. *Cell* 2013; **153**: 1239-1251 [PMID: 23746840 DOI: 10.1016/j.cell.2013.05.016]
- 133 **Zhang Y**, Kurupati R, Liu L, Zhou XY, Zhang G, Hudaihed A, Filisio F, Giles-Davis W, Xu X, Karakousis GC, Schuchter LM, Xu W, Amaravadi R, Xiao M, Sadek N, Krepler C, Herlyn M, Freeman GJ, Rabinowitz JD, Ertl HCJ. Enhancing CD8⁺ T Cell Fatty Acid Catabolism within a Metabolically Challenging Tumor Microenvironment Increases the Efficacy of Melanoma Immunotherapy. *Cancer Cell* 2017; **32**: 377-391.e9 [PMID: 28898698 DOI: 10.1016/j.ccell.2017.08.004]
- 134 **Wawman RE**, Bartlett H, Oo YH. Regulatory T Cell Metabolism in the Hepatic Microenvironment. *Front Immunol* 2018; **8**: 1889 [PMID: 29358934 DOI: 10.3389/fimmu.2017.01889]
- 135 **Beier UH**, Angelin A, Akimova T, Wang L, Liu Y, Xiao H, Koike MA, Hancock SA, Bhatti TR, Han R, Jiao J, Veasey SC, Sims CA, Baur JA, Wallace DC, Hancock WW. Essential role of mitochondrial energy metabolism in Foxp3⁺ T-regulatory cell function and allograft survival. *FASEB J* 2015; **29**: 2315-2326 [PMID: 25681462 DOI: 10.1096/fj.14-268409]
- 136 **Shirabe K**, Mano Y, Muto J, Matono R, Motomura T, Toshima T, Takeishi K, Uchiyama H, Yoshizumi T, Taketomi A, Morita M, Tsujitani S, Sakaguchi Y, Maehara Y. Role of tumor-associated macrophages in the progression of hepatocellular carcinoma. *Surg Today* 2012; **42**: 1-7 [PMID: 22116397 DOI: 10.1007/s00595-011-0058-8]
- 137 **Zhang J**, Zhang Q, Lou Y, Fu Q, Chen Q, Wei T, Yang J, Tang J, Wang J, Chen Y, Zhang X, Zhang J, Bai X, Liang T. Hypoxia-inducible factor-1 α /interleukin-1 β signaling enhances hepatoma epithelial-mesenchymal transition through macrophages in a hypoxic-inflammatory microenvironment. *Hepatology* 2018; **67**: 1872-1889 [PMID: 29171040 DOI: 10.1002/hep.29681]
- 138 **Clambey ET**, McNamee EN, Westrich JA, Glover LE, Campbell EL, Jedlicka P, de Zoeten EF, Cambier JC, Stenmark KR, Colgan SP, Eltzschig HK. Hypoxia-inducible factor-1 α -dependent induction of FoxP3 drives regulatory T-cell abundance and function during inflammatory hypoxia of the mucosa. *Proc Natl Acad Sci* 2012; **109**: E2784-E2793 [PMID: 22988108 DOI: 10.1073/pnas.1202366109]
- 139 **Chang M**, Hamilton JA, Scholz GM, Elsegood CL. Glycolytic control of adjuvant-induced macrophage survival: role of PI3K, MEK1/2, and Bcl-2. *J Leukoc Biol* 2009; **85**: 947-956 [PMID: 19270084 DOI: 10.1189/jlb.0908522]
- 140 **Sharma MD**, Shinde R, McGaha TL, Huang L, Holmgaard RB, Wolchok JD, Mautino MR, Celis E, Sharpe AH, Francisco LM, Powell JD, Yagita H, Mellor AL, Blazar BR, Munn DH. The PTEN pathway in Tregs is a critical driver of the suppressive tumor microenvironment. *Sci Adv* 2015; **1**: e1500845 [PMID: 26601142 DOI: 10.1126/sciadv.1500845]
- 141 **Chen W**, Ma T, Shen XN, Xia XF, Xu GD, Bai XL, Liang TB. Macrophage-induced tumor angiogenesis is regulated by the TSC2-mTOR pathway. *Cancer Res* 2012; **72**: 1363-1372 [PMID: 22287548 DOI: 10.1158/0008-5472.can-11-2684]
- 142 **Zeng H**, Yang K, Cloer C, Neale G, Vogel P, Chi H. mTORC1 couples immune signals and metabolic programming to establish T(reg)-cell function. *Nature* 2013; **499**: 485-490 [PMID: 23812589 DOI: 10.1038/nature12297]

P- Reviewer: Ooi LL, Rodríguez-Perálvarez M, Yamasaki T
S- Editor: Wang XJ **L- Editor:** Filipodia **E- Editor:** Huang Y





Published by **Baishideng Publishing Group Inc**
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: <http://www.f6publishing.com/helpdesk>
<http://www.wjgnet.com>



ISSN 1007-9327

