

World Journal of *Clinical Cases*

World J Clin Cases 2021 December 6; 9(34): 10392-10745



Contents

Thrice Monthly Volume 9 Number 34 December 6, 2021

OPINION REVIEW

- 10392** Regulating monocyte infiltration and differentiation: Providing new therapies for colorectal cancer patients with COVID-19

Bai L, Yang W, Qian L, Cui JW

REVIEW

- 10400** Role of circular RNAs in gastrointestinal tumors and drug resistance

Xi SJ, Cai WQ, Wang QQ, Peng XC

MINIREVIEWS

- 10418** Liver injury associated with acute pancreatitis: The current status of clinical evaluation and involved mechanisms

Liu W, Du JJ, Li ZH, Zhang XY, Zuo HD

- 10430** Association between celiac disease and vitiligo: A review of the literature

Zhang JZ, Abudoureyimu D, Wang M, Yu SR, Kang XJ

- 10438** Role of immune escape in different digestive tumours

Du XZ, Wen B, Liu L, Wei YT, Zhao K

ORIGINAL ARTICLE

Basic Study

- 10451** Magnolol protects against acute gastrointestinal injury in sepsis by down-regulating regulated on activation, normal T-cell expressed and secreted

Mao SH, Feng DD, Wang X, Zhi YH, Lei S, Xing X, Jiang RL, Wu JN

Case Control Study

- 10464** Effect of Nephritis Rehabilitation Tablets combined with tacrolimus in treatment of idiopathic membranous nephropathy

Ly W, Wang MR, Zhang CZ, Sun XX, Yan ZZ, Hu XM, Wang TT

Retrospective Cohort Study

- 10472** Lamb's tripe extract and vitamin B₁₂ capsule plus celecoxib reverses intestinal metaplasia and atrophy: A retrospective cohort study

Wu SR, Liu J, Zhang LF, Wang N, Zhang LY, Wu Q, Liu JY, Shi YQ

- 10484** Clinical features and survival of patients with multiple primary malignancies

Wang XK, Zhou MH

Retrospective Study

- 10494** Thoracoscopic segmentectomy and lobectomy assisted by three-dimensional computed-tomography bronchography and angiography for the treatment of primary lung cancer
Wu YJ, Shi QT, Zhang Y, Wang YL
- 10507** Endoscopic ultrasound fine needle aspiration *vs* fine needle biopsy in solid lesions: A multi-center analysis
Moura DTH, McCarty TR, Jirapinyo P, Ribeiro IB, Farias GFA, Madruga-Neto AC, Ryou M, Thompson CC
- 10518** Resection of bilateral occipital lobe lesions during a single operation as a treatment for bilateral occipital lobe epilepsy
Lyu YE, Xu XF, Dai S, Feng M, Shen SP, Zhang GZ, Ju HY, Wang Y, Dong XB, Xu B
- 10530** Improving rehabilitation and quality of life after percutaneous transhepatic cholangiography drainage with a rapid rehabilitation model
Xia LL, Su T, Li Y, Mao JF, Zhang QH, Liu YY
- 10540** Combined lumbar muscle block and perioperative comprehensive patient-controlled intravenous analgesia with butorphanol in gynecological endoscopic surgery
Zhu RY, Xiang SQ, Chen DR
- 10549** Teicoplanin combined with conventional vancomycin therapy for the treatment of pulmonary methicillin-resistant *Staphylococcus aureus* and *Staphylococcus epidermidis* infections
Wu W, Liu M, Geng JJ, Wang M
- 10557** Application of narrative nursing in the families of children with biliary atresia: A retrospective study
Zhang LH, Meng HY, Wang R, Zhang YC, Sun J

Observational Study

- 10566** Comparative study for predictability of type 1 gastric variceal rebleeding after endoscopic variceal ligation: High-frequency intraluminal ultrasound study
Kim JH, Choe WH, Lee SY, Kwon SY, Sung IK, Park HS
- 10576** Effects of WeChat platform-based health management on health and self-management effectiveness of patients with severe chronic heart failure
Wang ZR, Zhou JW, Liu XP, Cai GJ, Zhang QH, Mao JF
- 10585** Early cardiopulmonary resuscitation on serum levels of myeloperoxidase, soluble ST2, and hypersensitive C-reactive protein in acute myocardial infarction patients
Hou M, Ren YP, Wang R, Lu LX

Prospective Study

- 10595** Remimazolam benzenesulfonate anesthesia effectiveness in cardiac surgery patients under general anesthesia
Tang F, Yi JM, Gong HY, Lu ZY, Chen J, Fang B, Chen C, Liu ZY

Randomized Clinical Trial

- 10604** Effects of lower body positive pressure treadmill on functional improvement in knee osteoarthritis: A randomized clinical trial study
Chen HX, Zhan YX, Ou HN, You YY, Li WY, Jiang SS, Zheng MF, Zhang LZ, Chen K, Chen QX

SYSTEMATIC REVIEWS

- 10616** Effects of hypoxia on bone metabolism and anemia in patients with chronic kidney disease
Kan C, Lu X, Zhang R

META-ANALYSIS

- 10626** Intracuff alkalinized lidocaine to prevent postoperative airway complications: A meta-analysis
Chen ZX, Shi Z, Wang B, Zhang Y

CASE REPORT

- 10638** Rarely fast progressive memory loss diagnosed as Creutzfeldt-Jakob disease: A case report
Xu YW, Wang JQ, Zhang W, Xu SC, Li YX
- 10645** Diagnosis, fetal risk and treatment of pemphigoid gestationis in pregnancy: A case report
Jiao HN, Ruan YP, Liu Y, Pan M, Zhong HP
- 10652** Histology transformation-mediated pathological atypism in small-cell lung cancer within the presence of chemotherapy: A case report
Ju Q, Wu YT, Zhang Y, Yang WH, Zhao CL, Zhang J
- 10659** Reversible congestive heart failure associated with hypocalcemia: A case report
Wang C, Dou LW, Wang TB, Guo Y
- 10666** Excimer laser coronary atherectomy for a severe calcified coronary ostium lesion: A case report
Hou FJ, Ma XT, Zhou YJ, Guan J
- 10671** Comprehensive management of malocclusion in maxillary fibrous dysplasia: A case report
Kaur H, Mohanty S, Kochhar GK, Iqbal S, Verma A, Bhasin R, Kochhar AS
- 10681** Intravascular papillary endothelial hyperplasia as a rare cause of cervicothoracic spinal cord compression: A case report
Gu HL, Zheng XQ, Zhan SQ, Chang YB
- 10689** Proximal true lumen collapse in a chronic type B aortic dissection patient: A case report
Zhang L, Guan WK, Wu HP, Li X, Lv KP, Zeng CL, Song HH, Ye QL
- 10696** Tigecycline sclerotherapy for recurrent pseudotumor in aseptic lymphocyte-dominant vasculitis-associated lesion after metal-on-metal total hip arthroplasty: A case report
Lin IH, Tsai CH

- 10702** Acute myocardial infarction induced by eosinophilic granulomatosis with polyangiitis: A case report
Jiang XD, Guo S, Zhang WM
- 10708** Aggressive natural killer cell leukemia with skin manifestation associated with hemophagocytic lymphohistiocytosis: A case report
Peng XH, Zhang LS, Li LJ, Guo XJ, Liu Y
- 10715** Chronic lymphocytic leukemia/small lymphocytic lymphoma complicated with skin Langerhans cell sarcoma: A case report
Li SY, Wang Y, Wang LH
- 10723** Severe mediastinitis and pericarditis after endobronchial ultrasound-guided transbronchial needle aspiration: A case report
Koh JS, Kim YJ, Kang DH, Lee JE, Lee SI
- 10728** Obturator hernia - a rare etiology of lateral thigh pain: A case report
Kim JY, Chang MC
- 10733** Tracheal tube misplacement in the thoracic cavity: A case report
Li KX, Luo YT, Zhou L, Huang JP, Liang P
- 10738** Peri-implant keratinized gingiva augmentation using xenogeneic collagen matrix and platelet-rich fibrin: A case report
Han CY, Wang DZ, Bai JF, Zhao LL, Song WZ

ABOUT COVER

Editorial Board Member of *World Journal of Clinical Cases*, Gagan Mathur, MBBS, MD, Associate Professor, Director, Staff Physician, Department of Pathology, Saint Luke's Health System, Kansas City, MO 64112, United States. gmathur@saint-lukes.org

AIMS AND SCOPE

The primary aim of *World Journal of Clinical Cases* (WJCC, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

INDEXING/ABSTRACTING

The WJCC is now indexed in Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, PubMed, and PubMed Central. The 2021 Edition of Journal Citation Reports® cites the 2020 impact factor (IF) for WJCC as 1.337; IF without journal self cites: 1.301; 5-year IF: 1.742; Journal Citation Indicator: 0.33; Ranking: 119 among 169 journals in medicine, general and internal; and Quartile category: Q3. The WJCC's CiteScore for 2020 is 0.8 and Scopus CiteScore rank 2020: General Medicine is 493/793.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Yan-Xia Xing; Production Department Director: Yun-Jie Ma; Editorial Office Director: Jin-Lei Wang.

NAME OF JOURNAL

World Journal of Clinical Cases

ISSN

ISSN 2307-8960 (online)

LAUNCH DATE

April 16, 2013

FREQUENCY

Thrice Monthly

EDITORS-IN-CHIEF

Dennis A Bloomfield, Sandro Vento, Bao-Gan Peng

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

PUBLICATION DATE

December 6, 2021

COPYRIGHT

© 2021 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Role of immune escape in different digestive tumours

Xin-Zhu Du, Bin Wen, Lin Liu, Ying-Ting Wei, Kui Zhao

ORCID number: Xin-Zhu Du 0000-0003-0459-5024; Bin Wen 0000-0001-8413-0037; Lin Liu 0000-0001-7246-593X; Ying-Ting Wei 0000-0001-9434-7600; Kui Zhao 0000-0002-1639-0918.

Author contributions: Du XZ performed the literature search and wrote the manuscript; Wen B categorized the information; Liu L proofread the manuscript; Wei YT checked the information; and Zhao K revised the manuscript.

Conflict-of-interest statement: The authors have no conflicts of interest to disclose.

Country/Territory of origin: China

Specialty type: Immunology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution

Xin-Zhu Du, Bin Wen, Lin Liu, Ying-Ting Wei, Kui Zhao, Department of Gastroenterology, The Affiliated Hospital of Zunyi Medical University, Zunyi 563000, Guizhou Province, China

Corresponding author: Kui Zhao, MD, Doctor, Department of Gastroenterology, The Affiliated Hospital of Zunyi Medical University, No. 201 Dalian Road, Zunyi 563000, Guizhou Province, China. kuizhao95858@163.com

Abstract

A counterbalance between immune cells and tumour cells is key to fighting tumours, and immune escape is an important mechanism for the survival of tumour cells in the body. Tumor cells and their cytokines impair the activity of T cells, NK cells, macrophages and other immune cells through various ways, and change the expression of their own surface antigens so as to avoid the clearance of the immune system. Changes in major histocompatibility complex molecules, high expression of programmed death-ligand 1, and the presence of immunosuppressive cells in the tumor microenvironment (TME) are main means by which tumors impair the function of immune cells. During the development of tumours of the digestive system, different mechanisms acting on tumour cells, the TME, and immune cells lead to immune escape and promote tumour progression. In this paper, the mechanisms of immune escape in tumour cells of the digestive system are reviewed to provide a theoretical basis for the immunotherapy of gastrointestinal tumours.

Key Words: Gastrointestinal tumors; Immune escape; Immune cells; Tumor microenvironment; Molecular; Mechanism

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: To summarize and analyze the mechanisms of immune escape of tumor cells in the digestive system and provide help for immunotherapy. In this paper, the mechanisms can be analyzed from many aspects, including not only tumor cells themselves, but also immune cells and some other external factors. Through the summary of these mechanisms, we find some deficiencies in the research in this area, which may provide some ideas for the follow-up research.

Citation: Du XZ, Wen B, Liu L, Wei YT, Zhao K. Role of immune escape in different digestive tumours. *World J Clin Cases* 2021; 9(34): 10438-10450

NonCommercial (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/>

Received: July 25, 2021

Peer-review started: July 25, 2021

First decision: August 8, 2021

Revised: August 15, 2021

Accepted: October 18, 2021

Article in press: October 18, 2021

Published online: December 6, 2021

P-Reviewer: Wang Z, Zharikov YO

S-Editor: Yan JP

L-Editor: A

P-Editor: Yan JP



URL: <https://www.wjgnet.com/2307-8960/full/v9/i34/10438.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v9.i34.10438>

INTRODUCTION

Digestive tumours are diseases with a high incidence worldwide, and the pathogenesis, clinical manifestations, and treatment of these tumours have been studied extensively. However, despite increased awareness and early screening for digestive tumours, only a few patients with distant metastases, such as colorectal cancer (CRC)[1], have long-term survival; CRC has the third-highest incidence of common tumours in the world and is the fourth leading cause of tumour-related death worldwide[2]. Therefore, it is particularly important to treat digestive tumours based on the root causes or pathogenesis. In recent years, many pieces of evidence have been obtained that support the view that the immune system plays an important role in tumorigenesis. Evading the surveillance of the immune system is also considered one of the markers of tumours. Some scholars believe that cancer immune editing includes three consecutive stages: Elimination, balance, and escape[3]. During the transformation of adenomas into malignant tumours, adenomatous dysplasia may represent an equilibrium phase, and malignant tumours may occur in the escape phase. Tumour cells escape attack from the immune system mainly by changing biological characteristics and microenvironments. Additionally, external factors can participate in immune escape. The mechanisms by which digestive tumours evade immune attack are summarized below (see Table 1).

ALTERATIONS IN MAJOR HISTOCOMPATIBILITY COMPLEX MOLECULES INVOLVED IN IMMUNE ESCAPE

Major histocompatibility complex (MHC) is a protein complex loaded with short peptides on the cell surface that can be recognized by the T-cell receptor (TCR)[3,4]. Research shows that MHC-I molecules play an important role in the acquired immune response of vertebrates and the occurrence and development of digestive system tumours[5]. For example, HLA-G, a nonclassical MHC-class I molecule, has been demonstrated to be expressed in digestive system tumours[6]. HLA-G expression was first identified at the maternal-foetal interface of cytotrophoblast cells and was subsequently discovered to be involved in organ transplantation, malignant transformation, and autoimmune diseases, while allowing tumours or viruses to evade immune responses[7]. HLA-G exerts an inhibitory effect on NK cells, T lymphocytes, and antigen-presenting cells mainly by directly binding to the inhibitory receptors ILT-2, ILT-4, and KIR2DL4[8]. In addition, soluble HLA-G (sHLA-G) binds to CD8 helper receptors, leading to apoptosis of NK and T cells and weakening host immune defences[9].

Unlike HLA-G, which participates in immune escape by affecting immune cell function (mainly NK and T cells), HLA-I, a classical MHC molecule, downregulates its expression in tumour cells and reduces the expression of tumour-associated antigen (TAA) on the surface of tumour cells, thus evading recognition and attack by immune cells[10]. This process is one of the mechanisms by which oesophageal malignant tumour cells escape immune surveillance of CD8⁺ T cells[11]. For example, aflatoxin G1 precisely reduces the expression of immunoproteasome LMP-2 in oesophageal malignant tumour cells, and the resulting downregulation of HLA-I expression on the surface of tumour cells hinders the recognition of T lymphocytes and enables tumour cells to escape immune surveillance[12]. Downregulation or complete suppression of the HLA-I gene leads to inefficient antigen presentation and a decrease in the recognition rate of cytotoxic T lymphocytes (CTLs)[13], which suggests that the deletion of HLA-I molecules may be one of the advantages of the host evasion of immune defence. In studies on gastric malignancies associated with the Epstein-Barr virus (EBV) infection, it was found that microRNA encoded by EBV decreased the antigen presentation function of MHC-I molecules, thus enabling cells infected with EBV to escape the killing effect of immune cells[14]. MHC-II levels have also been found to be significantly higher in almost all EBV-related gastric malignancies than in normal tissues, unlike MHC-I levels[15]. This result suggests that the upregulation of the MHC-II molecule may also be involved in immune escape. The expression of HLA-

Table 1 The mechanisms of immune escape in different digestive tumours

Molecules/cells	Ref.	Tumor/cancer	Cells/cytokines	Up/down	Pathway/target	Outcomes
HLA-G	Bespalova <i>et al</i> [8], 2020; Liu <i>et al</i> [16], 2020	CRC	NK cells, T lymphocytes, and antigen-presenting cells	Up	ILT-2, ILT-4, and KIR2DL4	By directly binding to the inhibitory receptors ILT-2, ILT-4, and KIR2DL4, leading to apoptosis of NK and T cells and weakening host immune defences
HLA-I	Zhao <i>et al</i> [11], 2011; Li <i>et al</i> [12], 2010; Özgül Özdemir <i>et al</i> [19], 2016	Oesophageal malignant tumour, CRC	CD8 ⁺ T cells, T lymphocytes	Down	TAA	Downregulates the expression of HLA-I and reduces the expression of tumour-associated antigen (TAA) on the surface of tumour cells, evading recognition and attack by immune cells
HLA-E	Huang <i>et al</i> [17], 2017; Abd Hamid <i>et al</i> [18], 2019	Early CRC	CTLs and NK cells	Up	CD94/NKG2A	HLA-E is overexpressed on the surface of early CRC cells and can bind to the HLA-E receptor CD94/NKG2A, which is expressed on the surface of CTLs and NK cells, thus inhibiting their activity
PD-L1	Calderaro <i>et al</i> [27], 2016	Oesophageal carcinoma	EGFR	Up	PI3K/AKT, EGFR-RAS-RAF-ERK	Binding of the transmembrane protein - programmed death-ligand 1 (PD-L1) expressed in tumour cells or cells in the TME to PD-1 expressed on T cells can induce the production of immunosuppressive signals and decrease the proliferation of T cells, resulting in the depletion of T cells
	Liu <i>et al</i> [30], 2020	CRC	CCL5	Up	p65/STAT3-CSN5-PD-L1	Stabilizes PD-L1 in and out of cells through the p65/STAT3-CSN5-PD-L1 pathway mediated by NF-κB1 p65 (p65), which inhibits T-cell-mediated killing of HT29 tumour cells
	Ghedini <i>et al</i> [31], 2018	CRC	FGFR2	Up	JAK/STAT3	The tyrosine kinase domain initiates a series of intracellular signal cascade reactions, activates the JAK/STAT3 signalling pathway, and induces PD-L1 expression in CRC cells, thus participating in the occurrence and development of CRC
	Li <i>et al</i> [34], 2019	CRC	CXCL5	Up	PIK3/Akt	The binding of CXCL5 to CXCR2 on the surface of CRC cells promotes the movement of the CXCL5-CXCR2 axis, thus activating the PI3K/AKT signalling pathway and upregulating the expression of PD-L1 in CRC
	Li <i>et al</i> [38], 2019	Gallbladder malignant tumour	T cells	Up	PIK3/Akt	Upregulation of PD-L1 in gallbladder malignant tumour cells, activated the PIK3/Akt pathway, inhibited the cytotoxicity mediated by normal T cells, and promoted tumour growth and development
Galectin-9	Wang <i>et al</i> [41], 2016; Halama <i>et al</i> [43], 2011	Oesophageal carcinoma, CRC	NK cells	Down	Rho/ROCK-1, F-actin polarization	The low expression of Galectin-9 may lead to decreased activation or insufficient transport of NK cells to the tumour site
DKK2	Xiao <i>et al</i> [44], 2018	CRC	NK cells, CD8 ⁺ T cells	Up	STAT	The binding of DKK2 to LRP5 on the surface of NK cells leads to the disordering of STAT5 nuclear localization in NK cells and hinders the activation of NK cells
MDSCs	Geiger <i>et al</i> [53], 2016	CRC	T cells	Up	L-arginine	The high expression of MDSCs consumes a large quantity of L-arginine, and the resulting depletion of L-arginine affects T-cell proliferation
	Li <i>et al</i> [54], 2018	Oesophageal carcinoma	T cells	Up	Akt1/rela/IL8	Oesophageal malignant tumour cells can guide MDSCs to migrate to the tumour site and promote tumour progression by activating the Akt1/rela/IL8 signalling pathway
Treg cells	Chen <i>et al</i> [60], 2017	CRC	TCR	Up	CXCL13-CXCR5 axis	HDCC mainly promotes the infiltration of Treg cells by binding to CXCR5 on the surface of Treg cells by secreting CXCL13,

						which initiates the CXCL13-CXCR5 axis, promotes the proliferation of Treg cells and the aggregation of Treg cells at the tumour site
TIM-3	Shan <i>et al</i> [72], 2016	Oesophageal carcinoma	CD4 ⁺ Th1, CD8 ⁺ T cells, dysfunctional CD8 ⁺ T cells and FoxP3 ⁺ Treg cells	Up	AKT/GSK-3 β /Snail	A high expression of TIM-3 in tumour cells often indicates a poor prognosis of tumours
CD47	Fujiwara-Tani <i>et al</i> [76], 2019	Gastric tumour, CRC	Macrophages	Up	Sirp α	CD47 can prevent macrophage-mediated phagocytosis and antigen presentation by interacting with the receptor Sirp α expressed on macrophages, thus allowing tumour cells to escape the immune surveillance of macrophages
NF- κ B	Ouyang <i>et al</i> [83], 2021; He <i>et al</i> [84], 2021	Gallbladder malignant tumours, Pancreatic malignant tumours, CRC	T cell granzyme B gene	Up	Toll-like receptor 4, NF- κ B/p65	NF- κ B realizes the immune escape of tumour cells by affecting the transcription of effector T cells at the cellular transcriptional level. NF- κ B inhibits GZMB transcription in T cells, induces CTL dysfunction, and promotes tumour immune escape
IDO1 ⁺ Paneth cells	Mezrich <i>et al</i> [90], 2010	Oesophageal carcinoma, CRC	CD8 ⁺ T cells	Up	Canine uric acid, tryptophan	IDO facilitates immune escape by locally increasing the level of canine uric acid derived from tumour epithelial cells and consuming tryptophan. The increased level of canine uric acid promotes the differentiation of Treg cells through the aromatic hydrocarbon receptor AhR29, and the depletion of tryptophan can lead to cell cycle arrest of T cells, both of which can inhibit the antitumour immune response

G in CRC cells is associated with high tumour grades and poor prognosis[16]. In addition to HLA-G, the upregulation of another nonclassical MHC molecule, HLA-E, in CRC has also been confirmed to participate in immune escape. In contrast to HLA-G, HLA-E is primarily involved in the immunosuppressive response to early CRC[17]. HLA-E is overexpressed on the surface of early CRC cells and can bind to the HLA-E receptor CD94/NKG2A, which is expressed on the surface of CTLs and NK cells, thus inhibiting their activity[18]. Additionally, HLA-E expression can inhibit cetuximab-mediated antibody cytotoxicity and promote the immune escape of CRC[19]. Both nonclassical and classical MHC molecules, such as HLA-I, are expressed on CRC cells. Prognostic studies of patients with CRC suggest a poor overall survival rate in patients with deletion or downregulation of HLA-I[20]. This result supports the hypothesis that HLA-I is involved in immune escape. In a study on gastric cancer, patients with loss of expression of MHC-I molecules on the surface of tumour cells had shorter overall survival than those with normally expressed MHC-I molecules[21]. In pancreatic malignancies, tumour cells actively degrade MHC-I through the autophagy-lysosomal system, resulting in an MHC-I deficiency and providing favourable conditions for immune escape[22]. The alteration of MHC molecules has been found to significantly affect the immunogenicity of many gastrointestinal tumour cells. However, there is little evidence to support that changes in MHC molecules are involved in the immune escape of liver tumours, and further investigation is required to determine whether MHC molecules are involved in the tumour progression.

CYTOKINES INVOLVED IN IMMUNE ESCAPE

Tumor microenvironment (TME) consists of an extracellular matrix and mesenchymal cells, which produce cytokines that play an intermediary role in promoting tumour progression[23,24]. Binding of the transmembrane protein - programmed death-ligand 1 (PD-L1) expressed in tumour cells or cells in the TME to programmed death 1 (PD-1) expressed on T cells can induce the production of immunosuppressive signals and decrease the proliferation of T cells, resulting in the depletion of T cells. This binding process is one of the most important mechanisms of immune escape of tumour cells in the digestive system[25-27].

In the TME, the cytokines involved in the immune escape of tumour cells do not act directly on tumour cells but use signalling pathways to achieve PD-L1 upregulation

involved in immune escape *via* different mechanisms. In oesophageal malignancies, the activation of an EGFR-dependent PI3K/AKT pathway upregulates PD-L1 on the surface of tumour cells. In addition to the PI3K/AKT pathway, the upregulation of PD-L1 in oesophageal carcinoma is also affected by the EGFR-RAS-RAF-ERK and EGR-PLC- γ signalling pathways[28]. In gastric malignant tumour cells associated with EBV infection, the expression of PD-L1 is a common feature, and the overexpression of PD-L1 is associated with poor prognosis, but the mechanism is not clear. In addition, a significantly elevated PD-1⁺ lymphocyte count has been found in tumour stroma[29]. Some studies have shown a significant increase in the average expression level of PD-1 on T cells in peripheral blood and cancer tissues of patients with gastric cancer, suggesting that the PD-L1/PD-1 pathway is involved in immune escape in gastric cancer. Studies have also shown that a variety of cytokines participate in the immune escape process of CRC cells. For example, CCL5, a cytokine C-motif chemokine ligand 5 (CCL5) from tumour-associated macrophages (TAMs), stabilizes PD-L1 in and out of cells through the p65/STAT3-CSN5-PD-L1 pathway mediated by NF- κ B1 p65 (p65), which inhibits T-cell-mediated killing of HT29 tumour cells, which is key for CRC cells to escape immune surveillance[30]. Not only do TAMs participate in the upregulation of PD-L1, but TAM subtype M2 macrophages also participate in the upregulation of PD-1 expression, which promotes the binding of PD-L1/PD-1. In addition, in the TME, VEGF-c is a growth factor involved in tumour-associated lymphangiogenesis that can also promote M2-mediated immune escape by changing the density of TAMs, as well as increasing the percentage of M2/M1 macrophages in TAMs and the M2 survival rate. The tumour-derived fibroblast growth factor receptor (FGFR)-2 binds to ligand fibroblast growth factors (FGFs) in the tumour microenvironment and undergoes dimerization (receptor pairing). The tyrosine kinase domain initiates a series of intracellular signal cascade reactions, activates the JAK/STAT3 signalling pathway, and induces PD-L1 expression in CRC cells, thus participating in the occurrence and development of CRC[31,32]. PD-L1 and FGFR2 have been found to be overexpressed in CRC and positively correlated with each other[33]. It has also been observed that the overexpression of FGFR2 in CRC not only increased the apoptosis rate of T cells but was also correlated with lymph node metastasis, clinical stage cancer, and a poor survival rate. In addition to the JAK/STAT3 signalling pathway, the PIK3/Akt pathway, which has a high activation, is also one of the means of PD-L1 upregulation, with chemokine-5 (CXCL5) from cancer-associated fibroblasts (CAFs) as the medium [34,35]. CXCL5 is an effective cytokine that affects the TME in many ways, of which the PI3K/AKT signalling pathway is the most common. The binding of CXCL5 to CXCR2 on the surface of CRC cells promotes the movement of the CXCL5-CXCR2 axis, thus activating the PI3K/AKT signalling pathway and upregulating the expression of PD-L1 in CRC[36]. In liver tumour cells, the expression of PD-L1 decreases antitumour immune ability and promotes the immune escape of tumour cells[37]; PD-L1 expression has been shown to be related to the invasiveness of tumour cells[27]. It has also been observed that PD-L1 expression was upregulated in gallbladder malignant tumour cells, activated the PIK3/Akt pathway, inhibited the cytotoxicity mediated by normal T cells, and promoted tumour growth and development[38]. PD-L1 expression is higher in invasive pancreatic malignant tumours, and the non-Smad- β signalling pathway mediated by the transforming growth factor in the TME leads to more invasive phenotypes and immunosuppression mediated by PD-L1[39]. All these results confirm that PD-L1 is involved in the immune escape of digestive system tumours.

In some digestive system tumours (such as an oesophageal malignant tumour, CRC), some cytokines can also promote immune escape by affecting the function of immune cells. For example, Galectin-9 is a widely expressed protein in the TME that plays a dual role in the immune escape of tumour cells. Galectin-9 can not only affect the activity of NK cells through the signalling pathway mediated by TIM-3 (an immunosuppressive molecule) but can also bind to effector CD8⁺T cells expressing TIM-3 molecules in the TME, leading to apoptosis and promoting the occurrence of antitumour immunosuppression[40]. However, Galectin-9, as a protective factor against tumours, can also increase the recruitment of NK cells by affecting the expression of Rho/ROCK-1 and F-actin polarization[41]. Most tumour cells express Galectin-9 but at a lower positive rate and expression level than in normal tissues. In a prognostic study of patients with an oesophageal malignant tumour, it was found that low expression of Galectin-9 was closely related to poor prognosis[42]. These results suggest that the low expression of Galectin-9 may lead to decreased activation or insufficient transport of NK cells to the tumour site[43], which may be a new mechanism of tumour cell immune escape. In CRC, transcriptional activator (STAT) is the key regulator of NK cell functional activation, and dickkopf-associated protein 2

(DKK2), which is exploited *via* the high expression of a secretory protein in CRC tissue to affect the function of NK cells. The binding of DKK2 to LRP5 on the surface of NK cells leads to the disordering of STAT5 nuclear localization in NK cells and hinders the activation of NK cells[44]. DKK2 can also block the activation of CD8⁺ T cells, not by direct action on T cells but by indirect regulation of CD8⁺ T cells after direct interaction with NK cells[45]. In addition, DKK2 can inhibit the antitumour immune response by inhibiting the activation of CD8⁺ T cells mediated by IL-15[46].

Some studies have shown that, in addition to programmed death ligands, apoptosis antigen 1 (Fas) is also involved in the immune escape of digestive system tumours. Fas promotes apoptosis of tumour cells, whereas Fas ligand (FasL) has a protective effect on Fas-mediated apoptosis[17]. It has been found that FasL expressed by pancreatic tumor cells can avoid immune surveillance by inducing apoptosis of infiltrating lymphocytes around tumour tissue[47], but relatively few studies on FasL have been conducted to date.

IMMUNOSUPPRESSIVE CELLS INVOLVED IN IMMUNE ESCAPE

There are two important immunosuppressive cells in the TME, myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Treg cells). These two types of cells function both interdependently and independently during the process of suppression of antitumour immunity by digestive system tumour cells[48-50]. As the most common immunosuppressive cells, MDSCs exert inhibitory effects, such as on the production of anti-TAA antibodies and T cells and the function of NK cells, mainly through the transforming growth factor- β [51]. However, in digestive system tumours, MDSCs participate in immune escape mainly by inhibiting T-cell proliferation[52]. An important factor related to the inhibitory effect of MDSCs on T cells is L-arginine, an amino acid essential for T-cell proliferation and normal function. The high expression of MDSCs consumes a large quantity of L-arginine, and the resulting depletion of L-arginine affects T-cell proliferation[53]. Many scholars have confirmed that MDSCs are involved in the immune escape of digestive system tumours. Studies have shown that oesophageal malignant tumour cells can guide MDSCs to migrate to the tumour site and promote tumour progression by activating the Akt1/rela/IL8 signalling pathway [54]. The immunosuppressive effect of MDSCs on T cells in gastric tumour tissue has been related to the transforming growth factor β [55], and the upregulated expression of MDSCs in liver tumour cells has been related to poor prognosis[56].

In addition to affecting T-cell function, another important role of MDSCs is to stimulate the development of another key immunosuppressive cell, Treg cells, which can directly inhibit the TCR-mediated immune response, leading to antitumour suppression[57-59]. The CRC process involves another cell related to Treg cells, HDCC, a myeloid cell expressing histidine decarboxylase[60]. HDCC mainly promotes the infiltration of Treg cells by binding to CXCR5 on the surface of Treg cells by secreting CXCL13, which initiates the CXCL13-CXCR5 axis, promotes the proliferation of Treg cells and the aggregation of Treg cells at the tumour site. HDCC can also affect the function of Treg T cells directly or indirectly by regulating the function of CD8C T cells and thus plays an important role in inhibiting antitumour immunity. CD70⁺CAFs may also play a role in immune escape by promoting the aggregation of Treg cells and increasing the migration ability of Treg cells[61].

MDSCs and Treg cells complement each other. MDSCs can induce the production of Treg cells; conversely, Treg cells can stimulate the production of MDSCs through positive feedback of the transforming growth factor- β [51]. MDSCs can not only damage the activation of T cells by producing O₂ and iNOs but also cooperate with the VEGF to induce angiogenesis around tumour cells and directly stimulate tumour growth and metastasis[62-65]. In the TME, many favourable factors act as "fertile soil" for the growth of MDSCs to promote the immune escape of digestive system tumours. Factors such as PGE₂, IL-6, IL-10, LTB₄, and histamine are involved in the induction of MDSCs; local hypoxia and low pH in the TME can stimulate the expression of MDSCs, and S100A9 is a proinflammatory molecule that can induce an immunosuppressive microenvironment by regulating the chemotaxis and activation of MDSCs in digestive system tumours[66].

IMMUNOSUPPRESSIVE MOLECULES INVOLVED IN IMMUNE ESCAPE

Some immunosuppressive molecules in tumour cells, immune cells, and other immune-related cells, such as TIM-3, CD47, and NF- κ B, play a key role in the process of immune escape of tumours.

TIM-3 is a coinhibitory receptor that can be expressed not only in immune cells (including immunosuppressive cells) and tumour cells but also in other cells. TIM-3 acts as a negative regulator in immune cells (such as CD4⁺ Th1 and CD8⁺ T cells) and thus plays an important role in T-cell depletion in a variety of environments[67], whereas TIM-3 expression is promoted in immunosuppressive cells (such as dysfunctional CD8⁺ T cells and FoxP3⁺ Treg cells, two key cells in tumour development)[68, 69]. TIM-3 is also expressed in cell types other than the two abovementioned cell types [70], including myeloid cells and digestive system tumour cells themselves. A high expression of TIM-3 in tumour cells often indicates a poor prognosis of tumours[71], and studies have shown that TIM-3 can induce metastasis of oesophageal malignant tumours through the AKT/GSK-3 β /Snail signalling pathway[72]. In this regard, the TIM-3 molecule is a very suitable target for antitumour immunotherapy, and an in-depth study of TIM-3 may help identify new directions in immunotherapy.

The upregulation of CD47 expression in some digestive system tumours has been confirmed[73-75] and is closely related to the occurrence of gastric tumours associated with EBV infection[74]. CD47 can prevent macrophage-mediated phagocytosis and antigen presentation by interacting with the receptor Sirp α expressed on macrophages, thus allowing tumour cells to escape the immune surveillance of macrophages[76]. Furthermore, CD47 promotes the proliferation and metastasis of CRC cells by increasing aerobic glycolysis and activating the MAPK signalling pathway[77]. When blocking the PD-L1/PD-1 axis with an anti-PD-1 antibody, CD47Sirp α signal transduction can be weakened[78], suggesting that there may be a common pathway between the PD-L1/PD-1 axis and CD47-mediated immune escape, which is extremely significant for the further study of anti-immunotherapy.

Another common immunosuppressive molecule, NF- κ B, is widely found in tumour cells of the digestive system and participates in immune escape mainly by affecting the function of T cells. In a study on the effect of microtubule-associated serine/threonine kinase (MAST1) on gastric malignant tumours, it was found that tumour cells after MAST1 gene knockout exerted an antitumour effect by downregulating the expression of NF- κ B p65, suggesting that NF- κ B may be involved in the immune escape of tumour cells[79,80]. NF- κ B1 p50 (hereinafter referred to as p50) realizes the immune escape of tumour cells by affecting the transcription of effector T cells at the cellular transcriptional level[81,82]. P50 is a transcriptional inhibitor of the T cell granzyme B gene (GZMB). By binding to an unknown κ B element in the GZMB promoter, p50 inhibits GZMB transcription in T cells, induces CTL dysfunction, and promotes tumour immune escape. The activation of p50 and the expression of GZMB have been found to be negatively correlated with the degree of T-cell infiltration in CRC; that is, in CRC with a high level of p50 activation, the expression of GZMB was downregulated and T-cell infiltration decreased, whereas in CRC with a low level of p50 activation, the expression of GZMB was upregulated and T-cell infiltration increased. During the development of colitis into CRC, the colitis-related immune response may first activate p50 and damage the function of CTL effectors, leading to the immune escape of transformed epithelial cells and tumour development. In addition, in gallbladder malignant tumours, the downregulated expression of miR-146b-5p increases the expression of Toll-like receptor 4 (TLR4) and indirectly activates the NF- κ B signalling pathway, which regulates tumour development[83]. Tumour proliferation, epithelial transformation, and stem cell-like characteristics were found to be inhibited when the phosphorylation pathway of NF- κ B/p65 was blocked in pancreatic malignant tumour cells[84], which suggests that NF- κ B is involved in the development of pancreatic malignant tumours. Therefore, the activation of NF- κ B is considered to be a key link in the carcinogenesis of the human digestive system[85].

OTHER PROCESSES INVOLVED IN IMMUNE ESCAPE

The interaction between tumour cells and immune cells plays an important role in the occurrence of inflammation-related tumours. The reaction between tumour cells and immune cells has two facets: CTLs activated by antitumour action inhibit tumour growth, while chronic inflammation creates a microenvironment that promotes tumour cell growth and invasion. Studies have shown that an elevated level of the

inflammatory cytokine IL-6 can upregulate the expression of the cell adhesion molecule ICAM1 through the STAT3/5, ERK, and Rho-ROCK signalling pathways and promote the formation of chronic inflammation and lymphocyte death in tumour tissue, which enables the tumour to evade immune attack[86].

The inflammatory process induces tumour or immune cells to release cytokines[87] and is part of tumour immunosuppression, which plays an important role in tumour immune escape of the digestive system. In addition to the mechanism of the inflammatory reaction, another type of cell, the STAT1-dependent indole-2-dioxygenase-1 (IDO1)⁺ Paneth cell, plays an essential role in immune escape. In oesophageal malignant tumours, the expression of IDO has been found to impair the function of CD8⁺ T cells and promote the immune escape of oesophageal malignant tumours[88, 89]. IDO facilitates immune escape by locally increasing the level of canine uric acid derived from tumour epithelial cells and consuming tryptophan. The increased level of canine uric acid promotes the differentiation of Treg cells through the aromatic hydrocarbon receptor AhR29[90], and the depletion of tryptophan can lead to cell cycle arrest of T cells[91], both of which can inhibit the antitumour immune response. In addition, IDO participates in the immune escape of colitis-associated CRC, where IDO1⁺ Paneth cells exist in both cancer tissue and normal intestinal recess[92]. IDO1⁺ Paneth cells can be used as local immunosuppressants to prevent the abnormal activation of immune cells by bacteria and promote tumour progression.

In recent years, in-depth study of the digestive system has resulted in the identification of factors related to immune escape. For example, in a study on the relationship between intestinal flora and CRC, it was found that *Clostridium* could expand myeloid immune cells, inhibit the proliferation of T cells in CRC and induce T-cell apoptosis[93]. In blood circulation, platelets inhibit the immune response of T cells to CRC through the GARP-TGF- β axis; thus, drugs such as clopidogrel can improve the immunosuppressive response through antiplatelet aggregation[94]. In the TME, high levels of insulin and epidermal growth factor may be risk factors for tumour escape. When the TME is anoxic, lactic acid produced by tumour cells can weaken the differentiation and effector function of T cells and monocytes[95]. In addition, some RNAs can promote immune escape by affecting the function of immune cells. For example, microRNA-21 induces immunosuppression of CRC by increasing the levels of IL-10 and PGE2 (PGE2 inhibits DCs, macrophages, neutrophils, CTLs, TH1 cells, and NK cells and stimulates the production of MDSCs, Treg cells, and TH2)[96], and circRNA participates in the immune escape of liver tumour cells by regulating the function of NK cells[97].

CONCLUSION

The immune system is the body's protective barrier, and immune escape is really the umbrella for tumors. The immune escape of tumour cells in the digestive system is mainly realized by changing the expression of MHC molecules through various mechanisms; affecting the function of T cells, NK cells, and other immune cells; stimulating the activation and accumulation of immunosuppressive cells; and finally promote the immune escape of tumour cells, which is the key breakthrough of tumour immunotherapy. Among carcinogenic mechanisms, the immune escape mechanism of tumour cells provides a reliable basis for the further study of immunotherapy, which is expected to become a milestone in the history of tumour treatment that goes beyond surgical treatment, radiotherapy, and chemotherapy. Existing studies have confirmed that immune escape is involved in the development of most digestive system tumors, but it has been rarely reported in liver cancer, whether the immune escape is involved in the formation of it needs further study in the future. Although the development of digestive system tumours is closely related to the immune escape mechanism, it is difficult to block tumour progression at the root using a single locking mechanism; thus, many aspects and multiple dimensions of the immune escape mechanism need to be studied in the future. In-depth exploration of various mechanisms will help lay a theoretical foundation for further progress in immunotherapy.

ACKNOWLEDGEMENTS

The authors thank Professor Tuo BG (Department of Gastroenterology, Affiliated Hospital of Zunyi Medical College) for professional assistance.

REFERENCES

- 1 **Cao H**, Xu E, Liu H, Wan L, Lai M. Epithelial-mesenchymal transition in colorectal cancer metastasis: A system review. *Pathol Res Pract* 2015; **211**: 557-569 [PMID: [26092594](#) DOI: [10.1016/j.prp.2015.05.010](#)]
- 2 **Dekker E**, Tanis PJ, Vleugels JLA, Kasi PM, Wallace MB. Colorectal cancer. *Lancet* 2019; **394**: 1467-1480 [PMID: [31631858](#) DOI: [10.1016/S0140-6736\(19\)32319-0](#)]
- 3 **Rodríguez JA**. HLA-mediated tumor escape mechanisms that may impair immunotherapy clinical outcomes via T-cell activation. *Oncol Lett* 2017; **14**: 4415-4427 [PMID: [29085437](#) DOI: [10.3892/ol.2017.6784](#)]
- 4 **Zajonc DM**. Unconventional Peptide Presentation by Classical MHC Class I and Implications for T and NK Cell Activation. *Int J Mol Sci* 2020; **21** [PMID: [33066279](#) DOI: [10.3390/ijms21207561](#)]
- 5 **Kuznetsov A**, Voronina A, Govorun V, Arapidi G. Critical Review of Existing MHC I Immunoepitome Isolation Methods. *Molecules* 2020; **25** [PMID: [33228004](#) DOI: [10.3390/molecules25225409](#)]
- 6 **Swets M**, Seneby L, Boot A, van Wezel T, Gelderblom H, van de Velde CJ, van den Elsen PJ, Kuppen PJ. Promoter methylation and mRNA expression of HLA-G in relation to HLA-G protein expression in colorectal cancer. *Hum Immunol* 2016; **77**: 764-772 [PMID: [27245757](#) DOI: [10.1016/j.humimm.2016.05.023](#)]
- 7 **Xu X**, Zhou Y, Wei H. Roles of HLA-G in the Maternal-Fetal Immune Microenvironment. *Front Immunol* 2020; **11**: 592010 [PMID: [33193435](#) DOI: [10.3389/fimmu.2020.592010](#)]
- 8 **Bespalova O**, Bakleicheva M, Ivashchenko T, Tral T, Tolibova G, Kogan I. Expression of HLA-G and KIR2DL4 receptor in chorionic villous in missed abortion. *Gynecol Endocrinol* 2020; **36**: 43-47 [PMID: [33305671](#) DOI: [10.1080/09513590.2020.1816716](#)]
- 9 **Kirana C**, Ruszkiewicz A, Stubbs RS, Hardingham JE, Hewett PJ, Maddern GJ, Hauben E. Soluble HLA-G is a differential prognostic marker in sequential colorectal cancer disease stages. *Int J Cancer* 2017; **140**: 2577-2586 [PMID: [28233298](#) DOI: [10.1002/ijc.30667](#)]
- 10 **Swets M**, König MH, Zaalberg A, Dekker-Ensink NG, Gelderblom H, van de Velde CJ, van den Elsen PJ, Kuppen PJ. HLA-G and classical HLA class I expression in primary colorectal cancer and associated liver metastases. *Hum Immunol* 2016; **77**: 773-779 [PMID: [26968946](#) DOI: [10.1016/j.humimm.2016.03.001](#)]
- 11 **Zhao X**, Sun Q, Tian H, Cong B, Jiang X, Peng C. Loss of heterozygosity at 6p21 and HLA class I expression in esophageal squamous cell carcinomas in China. *Asian Pac J Cancer Prev* 2011; **12**: 2741-2745 [PMID: [22320985](#) DOI: [10.1007/978-3-642-16602-0_13](#)]
- 12 **Li Z**, Cui J, Zhang X, Kang W. Aflatoxin G1 reduces the molecular expression of HLA-I, TAP-1 and LMP-2 of adult esophageal epithelial cells in vitro. *Toxicol Lett* 2010; **195**: 169-173 [PMID: [20381597](#) DOI: [10.1016/j.toxlet.2010.03.1118](#)]
- 13 **Garrido F**. HLA Class-I Expression and Cancer Immunotherapy. *Adv Exp Med Biol* 2019; **1151**: 79-90 [PMID: [31140107](#) DOI: [10.1007/978-3-030-17864-2_3](#)]
- 14 **Ghasemi F**, Gameiro SF, Tessier TM, Maciver AH, Mymryk JS. High Levels of Class I Major Histocompatibility Complex mRNA Are Present in Epstein-Barr Virus-Associated Gastric Adenocarcinomas. *Cells* 2020; **9** [PMID: [32098275](#) DOI: [10.3390/cells9020499](#)]
- 15 **Ghasemi F**, Tessier TM, Gameiro SF, Maciver AH, Cecchini MJ, Mymryk JS. High MHC-II expression in Epstein-Barr virus-associated gastric cancers suggests that tumor cells serve an important role in antigen presentation. *Sci Rep* 2020; **10**: 14786 [PMID: [32901107](#) DOI: [10.1038/s41598-020-71775-4](#)]
- 16 **Liu L**, Wang L, Zhao L, He C, Wang G. The Role of HLA-G in Tumor Escape: Manipulating the Phenotype and Function of Immune Cells. *Front Oncol* 2020; **10**: 597468 [PMID: [33425752](#) DOI: [10.3389/fonc.2020.597468](#)]
- 17 **Huang R**, Zhang D, Li F, Xiao Z, Wu M, Shi D, Xiang P, Bao Z. Loss of Fas expression and high expression of HLA-E promoting the immune escape of early colorectal cancer cells. *Oncol Lett* 2017; **13**: 3379-3386 [PMID: [28521443](#) DOI: [10.3892/ol.2017.5891](#)]
- 18 **Abd Hamid M**, Wang RZ, Yao X, Fan P, Li X, Chang XM, Feng Y, Jones S, Maldonado-Perez D, Waugh C, Verrill C, Simmons A, Cerundolo V, McMichael A, Conlon C, Wang X, Peng Y, Dong T. Enriched HLA-E and CD94/NKG2A Interaction Limits Antitumor CD8⁺ Tumor-Infiltrating T Lymphocyte Responses. *Cancer Immunol Res* 2019; **7**: 1293-1306 [PMID: [31213473](#) DOI: [10.1158/2326-6066.CIR-18-0885](#)]
- 19 **Özgül Özdemir RB**, Özdemir AT, Oltulu F, Kurt K, Yiğittürk G, Kırmaz C. A comparison of cancer stem cell markers and nonclassical major histocompatibility complex antigens in colorectal tumor and noncancerous tissues. *Ann Diagn Pathol* 2016; **25**: 60-63 [PMID: [27806848](#) DOI: [10.1016/j.anndiagpath.2016.09.012](#)]
- 20 **Anderson P**, Aptsiauri N, Ruiz-Cabello F, Garrido F. HLA class I loss in colorectal cancer: implications for immune escape and immunotherapy. *Cell Mol Immunol* 2021; **18**: 556-565 [PMID: [33473191](#) DOI: [10.1038/s41423-021-00634-7](#)]
- 21 **Goepfert B**, Frauenschuh L, Zucknick M, Roessler S, Mehrabi A, Hafezi M, Stenzinger A, Warth A, Pathil A, Renner M, Schirmacher P, Weichert W. Major histocompatibility complex class I expression impacts on patient survival and type and density of immune cells in biliary tract cancer. *Br J Cancer* 2015; **113**: 1343-1349 [PMID: [26461054](#) DOI: [10.1038/bjc.2015.337](#)]
- 22 **Yamamoto K**, Venida A, Yano J, Biancur DE, Kakiuchi M, Gupta S, Sohn ASW, Mukhopadhyay S,

- Lin EY, Parker SJ, Banh RS, Paulo JA, Wen KW, Debnath J, Kim GE, Mancias JD, Fearon DT, Perera RM, Kimmelman AC. Autophagy promotes immune evasion of pancreatic cancer by degrading MHC-I. *Nature* 2020; **581**: 100-105 [PMID: 32376951 DOI: 10.1038/s41586-020-2229-5]
- 23 **Arneth B.** Tumor Microenvironment. *Medicina (Kaunas)* 2019; **56** [PMID: 31906017 DOI: 10.3390/medicina56010015]
- 24 **Zhang Y, Lou Y, Wang J, Yu C, Shen W.** Research Status and Molecular Mechanism of the Traditional Chinese Medicine and Antitumor Therapy Combined Strategy Based on Tumor Microenvironment. *Front Immunol* 2020; **11**: 609705 [PMID: 33552068 DOI: 10.3389/fimmu.2020.609705]
- 25 **Wang C, Weng M, Xia S, Zhang M, Chen C, Tang J, Huang D, Yu H, Sun W, Zhang H, Lai M.** Distinct roles of programmed death ligand 1 alternative splicing isoforms in colorectal cancer. *Cancer Sci* 2021; **112**: 178-193 [PMID: 33058325 DOI: 10.1111/cas.14690]
- 26 **Juneja VR, McGuire KA, Manguso RT, LaFleur MW, Collins N, Haining WN, Freeman GJ, Sharpe AH.** PD-L1 on tumor cells is sufficient for immune evasion in immunogenic tumors and inhibits CD8 T cell cytotoxicity. *J Exp Med* 2017; **214**: 895-904 [PMID: 28302645 DOI: 10.1084/jem.20160801]
- 27 **Calderaro J, Rousseau B, Amadeo G, Mercey M, Charpy C, Costentin C, Luciani A, Zafrani ES, Laurent A, Azoulay D, Lafdil F, Pawlowsky JM.** Programmed death ligand 1 expression in hepatocellular carcinoma: Relationship With clinical and pathological features. *Hepatology* 2016; **64**: 2038-2046 [PMID: 27359084 DOI: 10.1002/hep.28710]
- 28 **Zhang W, Pang Q, Yan C, Wang Q, Yang J, Yu S, Liu X, Yuan Z, Wang P, Xiao Z.** Induction of PD-L1 expression by epidermal growth factor receptor-mediated signaling in esophageal squamous cell carcinoma. *Onco Targets Ther* 2017; **10**: 763-771 [PMID: 28243112 DOI: 10.2147/OTT.S118982]
- 29 **Saito R, Abe H, Kunita A, Yamashita H, Seto Y, Fukayama M.** Overexpression and gene amplification of PD-L1 in cancer cells and PD-L1⁺ immune cells in Epstein-Barr virus-associated gastric cancer: the prognostic implications. *Mod Pathol* 2017; **30**: 427-439 [PMID: 27934877 DOI: 10.1038/modpathol.2016.202]
- 30 **Liu C, Yao Z, Wang J, Zhang W, Yang Y, Zhang Y, Qu X, Zhu Y, Zou J, Peng S, Zhao Y, Zhao S, He B, Mi Q, Liu X, Zhang X, Du Q.** Macrophage-derived CCL5 facilitates immune escape of colorectal cancer cells via the p65/STAT3-CSN5-PD-L1 pathway. *Cell Death Differ* 2020; **27**: 1765-1781 [PMID: 31802034 DOI: 10.1038/s41418-019-0460-0]
- 31 **Ghedini GC, Ronca R, Presta M, Giacomini A.** Future applications of FGF/FGFR inhibitors in cancer. *Expert Rev Anticancer Ther* 2018; **18**: 861-872 [PMID: 29936878 DOI: 10.1080/14737140.2018.1491795]
- 32 **Babina IS, Turner NC.** Advances and challenges in targeting FGFR signalling in cancer. *Nat Rev Cancer* 2017; **17**: 318-332 [PMID: 28303906 DOI: 10.1038/nrc.2017.8]
- 33 **Li P, Huang T, Zou Q, Liu D, Wang Y, Tan X, Wei Y, Qiu H.** FGFR2 Promotes Expression of PD-L1 in Colorectal Cancer via the JAK/STAT3 Signaling Pathway. *J Immunol* 2019; **202**: 3065-3075 [PMID: 30979816 DOI: 10.4049/jimmunol.1801199]
- 34 **Li Z, Zhou J, Zhang J, Li S, Wang H, Du J.** Cancer-associated fibroblasts promote PD-L1 expression in mice cancer cells via secreting CXCL5. *Int J Cancer* 2019; **145**: 1946-1957 [PMID: 30873585 DOI: 10.1002/ijc.32278]
- 35 **Yildirim K, Colak E, Aktimur R, Gun S, Taskin MH, Nigdelioglu A, Aktimur SH, Karagöz F, Ozlem N.** Clinical Value of CXCL5 for Determining of Colorectal Cancer. *Asian Pac J Cancer Prev* 2018; **19**: 2481-2484 [PMID: 30255816 DOI: 10.22034/apjcp.2018.19.9.2481]
- 36 **Sun X, Ng TTH, Sham KKY, Zhang L, Chan MTV, Wu WKK, Cheng CHK.** Bufalin, a Traditional Chinese Medicine Compound, Prevents Tumor Formation in Two Murine Models of Colorectal Cancer. *Cancer Prev Res (Phila)* 2019; **12**: 653-666 [PMID: 31431500 DOI: 10.1158/1940-6207.CAPR-19-0134]
- 37 **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]
- 38 **Li M, Liu F, Zhang F, Zhou W, Jiang X, Yang Y, Qu K, Wang Y, Ma Q, Wang T, Bai L, Wang Z, Song X, Zhu Y, Yuan R, Gao Y, Liu Y, Jin Y, Li H, Xiang S, Ye Y, Zhang Y, Jiang L, Hu Y, Hao Y, Lu W, Chen S, Gu J, Zhou J, Gong W, Wang X, Liu X, Liu C, Liu H.** Genomic *ERBB2/ERBB3* mutations promote PD-L1-mediated immune escape in gallbladder cancer: a whole-exome sequencing analysis. *Gut* 2019; **68**: 1024-1033 [PMID: 29954840 DOI: 10.1136/gutjnl-2018-316039]
- 39 **Hussain SM, Kansal RG, Alvarez MA, Hollingsworth TJ, Elahi A, Miranda-Carboni G, Hendrick LE, Pingili AK, Albritton LM, Dickson PV, Deneve JL, Yakoub D, Hayes DN, Kurosu M, Shibata D, Makowski L, Glazer ES.** Role of TGF- β in pancreatic ductal adenocarcinoma progression and PD-L1 expression. *Cell Oncol (Dordr)* 2021; **44**: 673-687 [PMID: 33694102 DOI: 10.1007/s13402-021-00594-0]
- 40 **Sasidharan Nair V, Toor SM, Taha RZ, Shaath H, Elkord E.** DNA methylation and repressive histones in the promoters of PD-1, CTLA-4, TIM-3, LAG-3, TIGIT, PD-L1, and galectin-9 genes in human colorectal cancer. *Clin Epigenetics* 2018; **10**: 104 [PMID: 30081950 DOI: 10.1186/s13148-018-0539-3]
- 41 **Wang Y, Sun J, Ma C, Gao W, Song B, Xue H, Chen W, Chen X, Zhang Y, Shao Q, Wang Q, Zhao L, Liu J, Wang X, Wang H, Yang M, Qu X.** Reduced Expression of Galectin-9 Contributes to a Poor Outcome in Colon Cancer by Inhibiting NK Cell Chemotaxis Partially through the Rho/ROCK1

- Signaling Pathway. *PLoS One* 2016; **11**: e0152599 [PMID: [27028892](#) DOI: [10.1371/journal.pone.0152599](#)]
- 42 **Hou N**, Ma J, Li W, Zhao L, Gao Q, Mai L. T-cell immunoglobulin and mucin domain-containing protein-3 and galectin-9 protein expression: Potential prognostic significance in esophageal squamous cell carcinoma for Chinese patients. *Oncol Lett* 2017; **14**: 8007-8013 [PMID: [29344243](#) DOI: [10.3892/ol.2017.7188](#)]
 - 43 **Halama N**, Braun M, Kahlert C, Spille A, Quack C, Rahbari N, Koch M, Weitz J, Kloor M, Zoernig I, Schirmacher P, Brand K, Grabe N, Falk CS. Natural killer cells are scarce in colorectal carcinoma tissue despite high levels of chemokines and cytokines. *Clin Cancer Res* 2011; **17**: 678-689 [PMID: [21325295](#) DOI: [10.1158/1078-0432.CCR-10-2173](#)]
 - 44 **Xiao Q**, Wu J, Wang WJ, Chen S, Zheng Y, Yu X, Meeth K, Sahraei M, Bothwell ALM, Chen L, Bosenberg M, Chen J, Sexl V, Sun L, Li L, Tang W, Wu D. DKK2 imparts tumor immunity evasion through β -catenin-independent suppression of cytotoxic immune-cell activation. *Nat Med* 2018; **24**: 262-270 [PMID: [29431745](#) DOI: [10.1038/nm.4496](#)]
 - 45 **Crouse J**, Xu HC, Lang PA, Oxenius A. NK cells regulating T cell responses: mechanisms and outcome. *Trends Immunol* 2015; **36**: 49-58 [PMID: [25432489](#) DOI: [10.1016/j.it.2014.11.001](#)]
 - 46 **Wu GZ**, Pan CX, Jiang D, Zhang Q, Li Y, Zheng SY. Clinicopathological significance of Fas and Fas ligand expressions in esophageal cancer. *Am J Cancer Res* 2015; **5**: 2865-2871 [PMID: [26609492](#)]
 - 47 **Lu C**, Paschall AV, Shi H, Savage N, Waller JL, Sabbatini ME, Oberlies NH, Pearce C, Liu K. The MLL1-H3K4me3 Axis-Mediated PD-L1 Expression and Pancreatic Cancer Immune Evasion. *J Natl Cancer Inst* 2017; **109** [PMID: [28131992](#) DOI: [10.1093/jnci/djw283](#)]
 - 48 **Karakasheva TA**, Waldron TJ, Eruslanov E, Kim SB, Lee JS, O'Brien S, Hicks PD, Basu D, Singhal S, Malavasi F, Rustgi AK. CD38-Expressing Myeloid-Derived Suppressor Cells Promote Tumor Growth in a Murine Model of Esophageal Cancer. *Cancer Res* 2015; **75**: 4074-4085 [PMID: [26294209](#) DOI: [10.1158/0008-5472.CAN-14-3639](#)]
 - 49 **Shitara K**, Nishikawa H. Regulatory T cells: a potential target in cancer immunotherapy. *Ann N Y Acad Sci* 2018; **1417**: 104-115 [PMID: [29566262](#) DOI: [10.1111/nyas.13625](#)]
 - 50 **Chang AL**, Miska J, Wainwright DA, Dey M, Rivetta CV, Yu D, Kanojia D, Pituch KC, Qiao J, Pytel P, Han Y, Wu M, Zhang L, Horbinski CM, Ahmed AU, Lesniak MS. CCL2 Produced by the Glioma Microenvironment Is Essential for the Recruitment of Regulatory T Cells and Myeloid-Derived Suppressor Cells. *Cancer Res* 2016; **76**: 5671-5682 [PMID: [27530322](#) DOI: [10.1158/0008-5472.Can-16-0144](#)]
 - 51 **Lee CR**, Kwak Y, Yang T, Han JH, Park SH, Ye MB, Lee W, Sim KY, Kang JA, Kim YC, Mazmanian SK, Park SG. Myeloid-Derived Suppressor Cells Are Controlled by Regulatory T Cells via TGF- β during Murine Colitis. *Cell Rep* 2016; **17**: 3219-3232 [PMID: [28009291](#) DOI: [10.1016/j.celrep.2016.11.062](#)]
 - 52 **Veglia F**, Perego M, Gabrilovich D. Myeloid-derived suppressor cells coming of age. *Nat Immunol* 2018; **19**: 108-119 [PMID: [29348500](#) DOI: [10.1038/s41590-017-0022-x](#)]
 - 53 **Geiger R**, Rieckmann JC, Wolf T, Basso C, Feng Y, Fuhrer T, Kogadeeva M, Picotti P, Meissner F, Mann M, Zamboni N, Sallusto F, Lanzavecchia A. L-Arginine Modulates T Cell Metabolism and Enhances Survival and Anti-tumor Activity. *Cell* 2016; **167**: 829-842.e13 [PMID: [27745970](#) DOI: [10.1016/j.cell.2016.09.031](#)]
 - 54 **Li P**, Chen X, Qin G, Yue D, Zhang Z, Ping Y, Wang D, Zhao X, Song M, Zhao Q, Li J, Liu S, Zhang C, Lian J, Cao L, Li F, Huang L, Wang L, Yang L, Huang J, Li H, Zhang B, Zhang Y. Maelstrom Directs Myeloid-Derived Suppressor Cells to Promote Esophageal Squamous Cell Carcinoma Progression via Activation of the Akt1/RelA/IL8 Signaling Pathway. *Cancer Immunol Res* 2018; **6**: 1246-1259 [PMID: [30082413](#) DOI: [10.1158/2326-6066.CIR-17-0415](#)]
 - 55 **Moaaz M**, Lotfy H, Elsherbini B, Motawea MA, Fadali G. TGF- β Enhances the Anti-inflammatory Effect of Tumor-Infiltrating CD33+11b+HLA-DR Myeloid-Derived Suppressor Cells in Gastric Cancer: A Possible Relation to MicroRNA-494. *Asian Pac J Cancer Prev* 2020; **21**: 3393-3403 [PMID: [33247701](#) DOI: [10.31557/APJCP.2020.21.11.3393](#)]
 - 56 **Ma C**, Zhang Q, Greten TF. MDSCs in liver cancer: A critical tumor-promoting player and a potential therapeutic target. *Cell Immunol* 2021; **361**: 104295 [PMID: [33508529](#) DOI: [10.1016/j.cellimm.2021.104295](#)]
 - 57 **Hanoteau A**, Newton JM, Krupar R, Huang C, Liu HC, Gaspero A, Gartrell RD, Saenger YM, Hart TD, Santegoets SJ, Laoui D, Spanos C, Parikh F, Jayaraman P, Zhang B, Van der Burg SH, Van Ginderachter JA, Melief CJM, Sikora AG. Tumor microenvironment modulation enhances immunologic benefit of chemoradiotherapy. *J Immunother Cancer* 2019; **7**: 10 [PMID: [30646957](#) DOI: [10.1186/s40425-018-0485-9](#)]
 - 58 **Fujimoto H**, Saito Y, Ohuchida K, Kawakami E, Fujiki S, Watanabe T, Ono R, Kaneko A, Takagi S, Najima Y, Hijikata A, Cui L, Ueki T, Oda Y, Hori S, Ohara O, Nakamura M, Saito T, Ishikawa F. Deregulated Mucosal Immune Surveillance through Gut-Associated Regulatory T Cells and PD-1⁺ T Cells in Human Colorectal Cancer. *J Immunol* 2018; **200**: 3291-3303 [PMID: [29581358](#) DOI: [10.4049/jimmunol.1701222](#)]
 - 59 **Langhans B**, Nischalke HD, Krämer B, Dold L, Lutz P, Mohr R, Vogt A, Toma M, Eis-Hübingen AM, Nattermann J, Strassburg CP, Gonzalez-Carmona MA, Spengler U. Role of regulatory T cells and checkpoint inhibition in hepatocellular carcinoma. *Cancer Immunol Immunother* 2019; **68**: 2055-2066 [PMID: [31724091](#) DOI: [10.1007/s00262-019-02427-4](#)]
 - 60 **Chen X**, Takemoto Y, Deng H, Middelhoff M, Friedman RA, Chu TH, Churchill MJ, Ma Y, Nagar

- KK, Tailor YH, Mukherjee S, Wang TC. Histidine decarboxylase (HDC)-expressing granulocytic myeloid cells induce and recruit Foxp3⁺ regulatory T cells in murine colon cancer. *Oncoimmunology* 2017; **6**: e1290034 [PMID: 28405523 DOI: 10.1080/2162402X.2017.1290034]
- 61 **Jacobs J**, Deschoolmeester V, Zwaenepoel K, Flieswasser T, Deben C, Van den Bossche J, Hermans C, Rolfo C, Peeters M, De Wever O, Lardon F, Siozopoulou V, Smits E, Pauwels P. Unveiling a CD70-positive subset of cancer-associated fibroblasts marked by pro-migratory activity and thriving regulatory T cell accumulation. *Oncoimmunology* 2018; **7**: e1440167 [PMID: 29900042 DOI: 10.1080/2162402X.2018.1440167]
- 62 **Hirsch L**, Flippot R, Escudier B, Albiges L. Immunomodulatory Roles of VEGF Pathway Inhibitors in Renal Cell Carcinoma. *Drugs* 2020; **80**: 1169-1181 [PMID: 32601914 DOI: 10.1007/s40265-020-01327-7]
- 63 **OuYang LY**, Wu XJ, Ye SB, Zhang RX, Li ZL, Liao W, Pan ZZ, Zheng LM, Zhang XS, Wang Z, Li Q, Ma G, Li J. Tumor-induced myeloid-derived suppressor cells promote tumor progression through oxidative metabolism in human colorectal cancer. *J Transl Med* 2015; **13**: 47 [PMID: 25638150 DOI: 10.1186/s12967-015-0410-7]
- 64 **Kumagai Y**, Tachikawa T, Higashi M, Sobajima J, Takahashi A, Amano K, Ishibashi KI, Mochiki E, Yakabi K, Tamaru JI, Ishida H. Chondromodulin-1 and vascular endothelial growth factor-A expression in esophageal squamous cell carcinoma: accelerator and brake theory for angiogenesis at the early stage of cancer progression. *Esophagus* 2020; **17**: 159-167 [PMID: 31595395 DOI: 10.1007/s10388-019-00695-8]
- 65 **Baba Y**, Nomoto D, Okadome K, Ishimoto T, Iwatsuki M, Miyamoto Y, Yoshida N, Baba H. Tumor immune microenvironment and immune checkpoint inhibitors in esophageal squamous cell carcinoma. *Cancer Sci* 2020; **111**: 3132-3141 [PMID: 32579769 DOI: 10.1111/cas.14541]
- 66 **Huang M**, Wu R, Chen L, Peng Q, Li S, Zhang Y, Zhou L, Duan L. S100A9 Regulates MDSCs-Mediated Immune Suppression via the RAGE and TLR4 Signaling Pathways in Colorectal Carcinoma. *Front Immunol* 2019; **10**: 2243 [PMID: 31620141 DOI: 10.3389/fimmu.2019.02243]
- 67 **Tang R**, Rangachari M, Kuchroo VK. Tim-3: A co-receptor with diverse roles in T cell exhaustion and tolerance. *Semin Immunol* 2019; **42**: 101302 [PMID: 31604535 DOI: 10.1016/j.smim.2019.101302]
- 68 **Liu JF**, Wu L, Yang LL, Deng WW, Mao L, Wu H, Zhang WF, Sun ZJ. Blockade of TIM3 relieves immunosuppression through reducing regulatory T cells in head and neck cancer. *J Exp Clin Cancer Res* 2018; **37**: 44 [PMID: 29506555 DOI: 10.1186/s13046-018-0713-7]
- 69 **Ono M**. Control of regulatory T-cell differentiation and function by T-cell receptor signalling and Foxp3 transcription factor complexes. *Immunology* 2020; **160**: 24-37 [PMID: 32022254 DOI: 10.1111/imm.13178]
- 70 **Das M**, Zhu C, Kuchroo VK. Tim-3 and its role in regulating anti-tumor immunity. *Immunol Rev* 2017; **276**: 97-111 [PMID: 28258697 DOI: 10.1111/imr.12520]
- 71 **Hong MH**, Shin SJ, Shin SK, Kim DJ, Zo JI, Shim YM, Lee SE, Cho BC, Park SY, Choi YL, Kim HR. High CD3 and ICOS and low TIM-3 expression predict favourable survival in resected oesophageal squamous cell carcinoma. *Sci Rep* 2019; **9**: 20197 [PMID: 31882943 DOI: 10.1038/s41598-019-56828-7]
- 72 **Shan B**, Man H, Liu J, Wang L, Zhu T, Ma M, Xv Z, Chen X, Yang X, Li P. TIM-3 promotes the metastasis of esophageal squamous cell carcinoma by targeting epithelial-mesenchymal transition via the Akt/GSK-3 β /Snail signaling pathway. *Oncol Rep* 2016; **36**: 1551-1561 [PMID: 27430162 DOI: 10.3892/or.2016.4938]
- 73 **Steinert G**, Schölch S, Niemietz T, Iwata N, García SA, Behrens B, Voigt A, Kloor M, Benner A, Bork U, Rahbari NN, Büchler MW, Stoecklein NH, Weitz J, Koch M. Immune escape and survival mechanisms in circulating tumor cells of colorectal cancer. *Cancer Res* 2014; **74**: 1694-1704 [PMID: 24599131 DOI: 10.1158/0008-5472.CAN-13-1885]
- 74 **Abe H**, Saito R, Ichimura T, Iwasaki A, Yamazawa S, Shinozaki-Ushiku A, Morikawa T, Ushiku T, Yamashita H, Seto Y, Fukayama M. CD47 expression in Epstein-Barr virus-associated gastric carcinoma: coexistence with tumor immunity lowering the ratio of CD8⁺/Foxp3⁺ T cells. *Virchows Arch* 2018; **472**: 643-651 [PMID: 29536167 DOI: 10.1007/s00428-018-2332-2]
- 75 **Rodríguez MM**, Fiore E, Bayo J, Atorrasagasti C, García M, Onorato A, Domínguez L, Malvicini M, Mazzolini G. 4Mu Decreases CD47 Expression on Hepatic Cancer Stem Cells and Primes a Potent Antitumor T Cell Response Induced by Interleukin-12. *Mol Ther* 2018; **26**: 2738-2750 [PMID: 30301668 DOI: 10.1016/j.ymthe.2018.09.012]
- 76 **Fujiwara-Tani R**, Sasaki T, Ohmori H, Luo Y, Goto K, Nishiguchi Y, Mori S, Nakashima C, Mori T, Miyagawa Y, Kawahara I, Fujii K, Kishi S, Tatsumoto N, Kuniyasu H. Concurrent Expression of CD47 and CD44 in Colorectal Cancer Promotes Malignancy. *Pathobiology* 2019; **86**: 182-189 [PMID: 31132784 DOI: 10.1159/000496027]
- 77 **Hu T**, Liu H, Liang Z, Wang F, Zhou C, Zheng X, Zhang Y, Song Y, Hu J, He X, Xiao J, King RJ, Wu X, Lan P. Tumor-intrinsic CD47 signal regulates glycolysis and promotes colorectal cancer cell growth and metastasis. *Theranostics* 2020; **10**: 4056-4072 [PMID: 32226539 DOI: 10.7150/thno.40860]
- 78 **Yu GT**, Bu LL, Huang CF, Zhang WF, Chen WJ, Gutkind JS, Kulkarni AB, Sun ZJ. PD-1 blockade attenuates immunosuppressive myeloid cells due to inhibition of CD47/SIRP α axis in HPV negative head and neck squamous cell carcinoma. *Oncotarget* 2015; **6**: 42067-42080 [PMID: 26573233 DOI: 10.18632/oncotarget.5955]

- 79 **An CX**, Xie SP, Li HL, Hu YH, Niu R, Zhang LJ, Jiang Y, Li Q, Zhou YN. Knockdown of Microtubule Associated Serine/threonine Kinase Like Expression Inhibits Gastric Cancer Cell Growth and Induces Apoptosis by Activation of ERK1/2 and Inactivation of NF- κ B Signaling. *Curr Med Sci* 2021; **41**: 108-117 [PMID: [33582914](#) DOI: [10.1007/s11596-021-2325-2](#)]
- 80 **Zhao H**, Xu J, Wang Y, Jiang R, Li X, Zhang L, Che Y. Knockdown of CEACAM19 suppresses human gastric cancer through inhibition of PI3K/Akt and NF- κ B. *Surg Oncol* 2018; **27**: 495-502 [PMID: [30217308](#) DOI: [10.1016/j.suronc.2018.05.003](#)]
- 81 **Suresh R**, Barakat DJ, Barberi T, Zheng L, Jaffee E, Pienta KJ, Friedman AD. NF- κ B p50-deficient immature myeloid cell (p50-IMC) adoptive transfer slows the growth of murine prostate and pancreatic ductal carcinoma. *J Immunother Cancer* 2020; **8** [PMID: [31940589](#) DOI: [10.1136/jitc-2019-000244](#)]
- 82 **Lu C**, Klement JD, Smith AD, Yang D, Waller JL, Browning DD, Munn DH, Liu K. p50 suppresses cytotoxic T lymphocyte effector function to regulate tumor immune escape and response to immunotherapy. *J Immunother Cancer* 2020; **8** [PMID: [33051343](#) DOI: [10.1136/jitc-2020-001365](#)]
- 83 **Ouyang B**, Pan N, Zhang H, Xing C, Ji W. miR146b5p inhibits tumorigenesis and metastasis of gallbladder cancer by targeting Tolllike receptor 4 via the nuclear factor κ B pathway. *Oncol Rep* 2021; **45** [PMID: [33649824](#) DOI: [10.3892/or.2021.7966](#)]
- 84 **He Y**, Peng X, Zheng L, Tang Y, Li J, Huang X. Asiaticoside inhibits epithelial-mesenchymal transition and stem cell-like properties of pancreatic cancer PANC-1 cells by blocking the activation of p65 and p38MAPK. *J Gastrointest Oncol* 2021; **12**: 196-206 [PMID: [33708436](#) DOI: [10.21037/jgo-20-533](#)]
- 85 **Mortezaee K**, Najafi M, Farhood B, Ahmadi A, Shabeeb D, Musa AE. NF- κ B targeting for overcoming tumor resistance and normal tissues toxicity. *J Cell Physiol* 2019; **234**: 17187-17204 [PMID: [30912132](#) DOI: [10.1002/jcp.28504](#)]
- 86 **Wang S**, Li L, Zhou Y, He Y, Wei Y, Tao A. Heterotypic cell-in-cell structures in colon cancer can be regulated by IL-6 and lead to tumor immune escape. *Exp Cell Res* 2019; **382**: 111447 [PMID: [31150612](#) DOI: [10.1016/j.yexcr.2019.05.028](#)]
- 87 **Huang HW**, Chang CC, Wang CS, Lin KH. Association between Inflammation and Function of Cell Adhesion Molecules Influence on Gastrointestinal Cancer Development. *Cells* 2021; **10** [PMID: [33406733](#) DOI: [10.3390/cells10010067](#)]
- 88 **Loeser H**, Kraemer M, Gebauer F, Bruns C, Schröder W, Zander T, Alakus H, Hoelscher A, Buettner R, Lohneis P, Quaas A. Indoleamine 2,3-Dioxygenase (IDO) Expression Is an Independent Prognostic Marker in Esophageal Adenocarcinoma. *J Immunol Res* 2020; **2020**: 2862647 [PMID: [33029538](#) DOI: [10.1155/2020/2862647](#)]
- 89 **Zhou S**, Zhao L, Liang Z, Liu S, Li Y, Yang H, Liu M, Xi M. Indoleamine 2,3-dioxygenase 1 and Programmed Cell Death-ligand 1 Co-expression Predicts Poor Pathologic Response and Recurrence in Esophageal Squamous Cell Carcinoma after Neoadjuvant Chemoradiotherapy. *Cancers (Basel)* 2019; **11** [PMID: [30717285](#) DOI: [10.3390/cancers11020169](#)]
- 90 **Mezrich JD**, Fechner JH, Zhang X, Johnson BP, Burlingham WJ, Bradfield CA. An interaction between kynurenine and the aryl hydrocarbon receptor can generate regulatory T cells. *J Immunol* 2010; **185**: 3190-3198 [PMID: [20720200](#) DOI: [10.4049/jimmunol.0903670](#)]
- 91 **Platten M**, Nollen EAA, Röhrig UF, Fallarino F, Opitz CA. Tryptophan metabolism as a common therapeutic target in cancer, neurodegeneration and beyond. *Nat Rev Drug Discov* 2019; **18**: 379-401 [PMID: [30760888](#) DOI: [10.1038/s41573-019-0016-5](#)]
- 92 **Pflügler S**, Svinka J, Scharf I, Crncec I, Filipits M, Charoentong P, Tschurtschenthaler M, Kenner L, Awad M, Stift J, Scherthanner M, Bissl R, Herndl-Brandstetter D, Glitzner E, Moll HP, Casanova E, Timelthaler G, Sibilia M, Gnant M, Lax S, Thaler J, Müller M, Strobl B, Mohr T, Kaser A, Trajanoski Z, Heller G, Eferl R. IDO1⁺ Paneth cells promote immune escape of colorectal cancer. *Commun Biol* 2020; **3**: 252 [PMID: [32444775](#) DOI: [10.1038/s42003-020-0989-y](#)]
- 93 **Nosho K**, Sukawa Y, Adachi Y, Ito M, Mitsuhashi K, Kurihara H, Kanno S, Yamamoto I, Ishigami K, Igarashi H, Maruyama R, Imai K, Yamamoto H, Shinomura Y. Association of Fusobacterium nucleatum with immunity and molecular alterations in colorectal cancer. *World J Gastroenterol* 2016; **22**: 557-566 [PMID: [26811607](#) DOI: [10.3748/wjg.v22.i2.557](#)]
- 94 **Servais L**, Wéra O, Dibato Epoh J, Delierneux C, Bouznad N, Rahmouni S, Mazzucchelli G, Baiwir D, Delvenne P, Lancellotti P, Oury C. Platelets contribute to the initiation of colitis-associated cancer by promoting immunosuppression. *J Thromb Haemost* 2018; **16**: 762-777 [PMID: [29369476](#) DOI: [10.1111/jth.13959](#)]
- 95 **Deng J**, Li J, Sarde A, Lines JL, Lee YC, Qian DC, Pechenick DA, Manivanh R, Le Mercier I, Lowrey CH, Varn FS, Cheng C, Leib DA, Noelle RJ, Mabaera R. Hypoxia-Induced VISTA Promotes the Suppressive Function of Myeloid-Derived Suppressor Cells in the Tumor Microenvironment. *Cancer Immunol Res* 2019; **7**: 1079-1090 [PMID: [31088847](#) DOI: [10.1158/2326-6066.CIR-18-0507](#)]
- 96 **Liu H**, Wang J, Tao Y, Li X, Qin J, Bai Z, Chi B, Yan W, Chen X. Curcumin inhibits colorectal cancer proliferation by targeting miR-21 and modulated PTEN/PI3K/Akt pathways. *Life Sci* 2019; **221**: 354-361 [PMID: [30811964](#) DOI: [10.1016/j.lfs.2019.02.049](#)]
- 97 **Tang Y**, Jiang M, Jiang HM, Ye ZJ, Huang YS, Li XS, Qin BY, Zhou RS, Pan HF, Zheng DY. The Roles of circRNAs in Liver Cancer Immunity. *Front Oncol* 2020; **10**: 598464 [PMID: [33614486](#) DOI: [10.3389/fonc.2020.598464](#)]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

