Role of immune escape in different digestive tumours

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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

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

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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
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, IL-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 et al [8], 2020; Liu et al [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 et al [11], 2011; Li et al [17], 2010; Özgül Özdemir et al [19], 2019 | 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 et al [17], 2017; Abd Hamid et al [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 et al [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 et al [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 IFN-αβ p65 (p65), which inhibits T-cell-mediated killing of HT29 tumour cells |
|                | Ghedini et al [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 et al [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 PIK3/Akt signalling pathway and upregulating the expression of PD-L1 in CRC |
| Galectin-9     | Wang et al [41], 2016; Halama et al [42], 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 et al [44], 2018 | CRC | NK cells, CD8⁺ T cells | Up | STAT | The binding of DKK2 to LRPs 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 et al [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 et al [54], 2018 |
| Oesophageal carcinoma | T cells | Up | Akt1/rela/IL8 | Oesophageal malignant tumour cells can upregulate MDSCs to migrate to the tumour site and promote tumour progression by activating the Akt1/rela/IL8 signalling pathway |
| Treg cells     | Chen et al [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,
| TIM-3 | Shan et al [72], 2016 | Oesophageal carcinoma | CD4^+ Th1, CD8^+ T cells, dysfunctional CD8^+ T cells and FoxP3^+ Treg cells | Up | AKT/GSK-3 β/Smad | A high expression of TIM-3 in tumour cells often indicates a poor prognosis of tumours |
|-------|-----------------------|-----------------------|-------------------------------------------------|----|----------------|--------------------------------------------------|
| CD47  | Fujiiwara-Tani et al [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-κB | Ouyang et al [85], 2021; He et al [86], 2021 | Gallbladder malignant tumours, Pancreatic malignant tumours, CRC | T cell granzyme B gene | Up | Toll-like receptor 4, NF-κB/p65 | NF-κB realizes the immune escape of tumour cells by affecting the transcription of effector T cells at the cellular transcriptional level. NF-κB inhibits GZMB transcription in T cells, induces CTL dysfunction, and promotes tumour immune escape |
| IDO1^+ Paneth cells | Mezrich et al [96], 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-kxB1 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 cells directly or indirectly by regulating the function of CD8+ 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-kB, play a key role in the process of immune escape of tumours.

TIM-3 is a co-inhibitory 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-3β/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, CD47/Sirp 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-xB, 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-xB p65, suggesting that NF-xB may be involved in the immune escape of tumour cells[79,80]. NF-kB 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 κB 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-xB 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-xB/p65 was blocked in pancreatic malignant tumour cells[84], which suggests that NF-xB is involved in the development of pancreatic malignant tumours. Therefore, the activation of NF-kB 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 anti-tumour 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-b 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 tumours, 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.
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