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REVIEW

Mechanisms of tumor immunosuppressive microenvironment formation in esophageal cancer

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Abstract

As a highly invasive malignancy, esophageal cancer (EC) is a global health issue, and was the eighth most prevalent cancer and the sixth leading cause of cancer-related death worldwide in 2020. Due to its highly immunogenic nature, emerging immunotherapy approaches, such as immune checkpoint blockade, have demonstrated promising efficacy in treating EC; however, certain limitations and challenges still exist. In addition, tumors may exhibit primary or acquired resistance to immunotherapy in the tumor immune microenvironment (TIME); thus, understanding the TIME is urgent and crucial, especially given the importance of an immunosuppressive microenvironment in tumor progression. The aim of this review was to better elucidate the mechanisms of the suppressive TIME, including cell infiltration, immune cell subsets, cytokines and signaling pathways in the tumor microenvironment of EC patients, as well as the downregulated expression of major histocompatibility complex molecules in tumor cells, to obtain a better understanding of the differences in EC patient responses to immunotherapeutic strategies and accurately predict the efficacy of immunotherapies. Therefore, personalized treatments could be developed to maximize the advantages of immunotherapy.

Key Words: Esophageal cancer; Esophageal squamous cell carcinoma; Esophageal adenocarcinoma; Tumor immune microenvironment; Immunosuppression; Immunotherapy

Core Tip: Esophageal cancer (EC) is a significant global health issue, and immunotherapy holds promise for treating this disease. However, resistance to immunotherapy may occur, and is usually associated with the tumor immune microenvironment (TIME). Understanding the TIME, especially the suppressive TIME, is crucial. The aim of this review is to elucidate the underlying mechanisms of the suppressive TIME in EC, including cell infiltration, immune cell subsets, cytokines and signaling pathways, as well as the downregulated expression of major histocompatibility complex molecules in tumor cells. This summary may help predict EC patient responses to immunotherapies and facilitate personalized treatments to optimize immunotherapeutic outcomes.

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INTRODUCTION

According to the Global Cancer Statistics 2020 database (https://gco.iarc.fr/), approximately 20000000 people are diagnosed with cancer each year, and approximately 10000000 people die from cancer worldwide[1]. Esophageal cancer (EC) accounts for 3.1% of all new cancer cases and ranks eighth in incidence among all cancer types; however, EC accounts for 5.5% of all cancer-related deaths and ranks sixth in mortality[1]. There are two main histological types of EC: Esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC)[2]. Although nearly 90% of EC cases are ESCC, the incidence and mortality rates of EAC are gradually increasing and even surpass those of ESCC in some regions of North America and Europe[3,4]. The main risk factors for EAC include gastroesophageal reflux disease and obesity, and ESCC is associated with chemical carcinogen exposure, cigarette smoking and alcohol consumption, a diet with low amounts of fruits or vegetables, high consumption of pickled vegetables or processed meat, hot drinks, *etc* [3,5]. The five-year survival rate of patients with EC is usually between 20% and 30%, and mainly depends on the tumor stage at initial diagnosis and the therapeutic strategy, such as surgery combined with neoadjuvant therapy (radiotherapy and chemotherapy)[6-8]. Since conventional treatments have limited efficacy and potential adverse effects, more effective therapeutic strategies are urgently needed to improve the prognosis of patients with EC[9].

Cancer development is closely related to the accumulation of gene mutations, and researchers have focused on changes in cancer cells for quite a long time[10]. Recently, the tumor microenvironment (TME) has become a hot topic, and the regulation of immune cells in the TME has drawn much attention[11]. The immune system can recognize and eliminate tumor cells expressing specific antigens, a process known as cancer immunosurveillance[12]; while, cancer cells can escape or suppress attacks from the immune system by various mechanisms, including decreasing antigen presentation, upregulating the expression of apoptotic inhibitors, increasing the expression of inhibitory molecules on the cell surface, and enhancing the secretion of certain cytokines or recruitment of regulatory cells to create an immunosuppressive microenvironment[12]. As an important component of the TME, the tumor immune microenvironment (TIME) refers to the microenvironment involving interactions between host immune agents and tumor cells[13,14]; tumors may confront host immune systems by gradually forming immunosuppressive conditions, and the presence of protumor and antitumor factors in the TIME may determine cancer progression and response to treatments[14-16]. Therefore, a comprehensive understanding of the interactions between tumor cells and various immune cells or other immune components in the TIME is vital for further elucidating the mechanisms of EC immunotherapy[17-20].

In this review, we mainly summarize the mechanisms of immunosuppression in the TIME of EC, including immune cells, immune checkpoints, immunosuppressive cells and tumor cell-related immunosuppressive factors, to provide evidence for the maintenance of an immune-activated state in the TIME of EC, with the goal of improving immunotherapeutic efficacy.

IMMUNOGENICITY OF ESOPHAGEAL CANCER

Esophageal epithelial tumor cells are the main constituents of EC and express tumor-associated antigens (TAAs)[19]. TAAs are a class of overexpressed molecules that are present mainly on the membrane of tumor cells, and are usually expressed at lower levels or undetected in normal cells[21]. T lymphocytes may recognize and bind the TAA peptides presented by major histocompatibility complex (MHC) molecules on tumor cells through the T-cell receptor, thereby initiating an immune response and triggering an attack on tumor cells[21]. In addition, natural killer (NK) lymphocytes and B lymphocytes play important roles in the regulation of immunoreactivity in EC[22,23]. For example, as a class of TAAs associated with 276 genes in more than 70 gene families, the antigen families formed by cancer-testis antigens (CTAs) are expressed mainly in ovarian granulosa cells and testicular germ cells, and are barely expressed in normal tissues[24-26]. Certain CTAs, such as New York ESCC 1 (NY-ESO-1) and melanoma-associated antigen-A (MAGE-A), have been reported to be highly expressed in EC, and specific immune responses targeting MAGE-A and NY-ESO-1 have been observed in EC patients[27-30]. MAGE-A3-specific $CD8^+$ T cells may kill HLA-$A2^+$/MAGE-$A3^+$ tumor cells in ESCC patients, and functional MAGE-C2-specific $CD8^+$ T cells may independently affect the prognosis of EC patients[27,31].

Since EC cells possess high immunogenicity, partially because of the presence of numerous antigens, these molecules could be potential targets for immunotherapy, and immunotherapy has been shown to be more effective in EC patients with an immuno-activated TME, leading to an improved prognosis[32]. However, current immunotherapeutic strategies have several limitations, *e.g.*, accompanying adverse effects and drug resistance cannot be avoided[33]. Therefore, a comprehensive understanding of the underlying mechanisms of the TIME in EC, especially the suppressive TIME, is pivotal and urgent for the management of EC patients.

DYSFUNCTION OF IMMUNE CELLS

A suppressive TIME is usually accompanied by the reduced infiltration or exhaustion of immune cells, and is correlated mainly with the presence of immunosuppressive cells and coinhibitory signals[34]. Herein, we focused on the reduced infiltration and exhaustion of T cells and NK cells, which play important roles in the TIME. In addition, immunosuppressive cells, such as suppressive macrophages (M2 macrophages) and myeloid-derived suppressor cells (MDSCs), can inhibit the activities of immune cells through various mechanisms to participate in balancing immune reactions in the TIME[35], and their presence may influence immunotherapeutic efficacy in cancers. Thus, elucidating the underlying molecular mechanisms is highly important for improving the therapeutic efficacy of agents for cancer treatment.

T lymphocytes

T cells are the major component of infiltrated immune cells in most solid tumors, and $CD8^+$ cytotoxic T cells (CTLs) and $CD4^+$ T helper cells (Ths) play crucial roles in eliminating tumor cells[36,37]. Specifically, activated CTLs may exert a cytotoxic effect on tumor cells by releasing cytotoxic substances, and Ths can promote or suppress host immune activities targeting tumor cells[36-38].

According to the single-cell sequencing results, the percentage of exhausted $CD8^+$ T cells positive for C-X-C motif chemokine ligand 13 (CXCL13) increased, as these cells are the main T-cell type in the TME of EAC patients[39]. In ESCC, the infiltration and proliferation of T-cell clones have also been observed, and an exhausted $CD8^+$ T-cell cluster (CD8-C7-TIGIT) and pre-exhausted CD8-C5-CCL5 and CD8-C6-STMN1 clusters accounted for high proportions of $CD8^+$ T-cell clusters[22]. The expression level of the E3 ubiquitin ligase MARCH7 in ESCC tissues has been shown to be significantly greater than that in nontumor tissues, and was negatively correlated with tumor-infiltrating immune cells, such as $CD8^+$ T cells[40]. Moreover, a subpopulation of $CD8^+$ T cells expressing SPRY1 has been found in ESCC tissues after neoadjuvant immune checkpoint blockade, and these cells may possess certain progenitor cell characteristics and exhibit an exhausted phenotype[41]. Additionally, fibroblast growth factor 2 derived from tumor fibroblasts can induce the expression of SPRY1 in infiltrating T cells and participate in T-cell exhaustion in EC[42].

Immune checkpoints: Activated T cells may express various inhibitory receptors, known as immune checkpoints, to prevent excessive immune responses, aiming to maintain an immunologic balance; however, tumor cells may exploit these checkpoints to induce coinhibitory signals in the TME and create an immunosuppressive TME, which plays a pivotal role in tumor immune escape[43,44]. Thus, medications such as immune checkpoint inhibitors have been investigated for their ability to block these checkpoints, subsequently enhancing the ability of the immune system to attack tumor cells[34,45].

Programmed cell death protein 1 (PD-1), which is expressed on the T-cell membrane, is a classic immune checkpoint that can transmit immune inhibitory signals when it interacts with its corresponding ligand programmed cell death ligand 1 (PD-L1), which is expressed on tumor cells[46,47]. These interactions can inhibit the cytotoxic activities of T cells and allow tumor cells to escape immune surveillance and attack, accounting for one of the mechanisms of tumor immune escape[46,47]. For instance, EC patients with high PD-L1/PD-L2 expression, particularly patients in advanced stages, may have a poor prognosis[20]. Therefore, inhibiting PD-1/PD-L1 by blocking their interaction may restore the vigor and cytotoxicity of T cells in the TIME[18]. In recent years, immunotherapy involving checkpoint blockade targeting PD-1/PD-L1 has developed rapidly, becoming a first-line treatment for many cancers[17,48], but the efficacy of PD-1/PD-L1 blockade largely depends on the expression levels of PD-1/PD-L1 in the TME[19,49,50].

The interaction between CD28 on T cells and B7-1 (CD80)/B7-2 (CD86) on antigen-presenting cells or target cells can provide costimulatory activating signals to T cells, and subsequently boost T-cell activation[51]. Cytolytic T lymphocyte-associated antigen-4 (CTLA-4), another important regulatory molecule primarily expressed on regulatory T cells (Tregs) and activated T cells, can competitively bind B7 and inhibit cellular signal transduction for T-cell activation, subsequently suppressing immune responses[52,53]. Therefore, CTLA-4 is also considered an immune checkpoint molecule, and CTLA-4 blockade could effectively enhance immune responses against tumor cells[52]. However, the efficacy and safety of CTLA-4 blockade in EC patients require further investigation due to the limited number of related clinical trials.

In addition to the coinhibitory molecules mentioned above[18,52,54,55], researchers have identified various other immune checkpoints, such as T-cell immunoglobulin (Ig) and mucin domain-containing protein-3 (TIM-3)[56,57], lymphocyte activation gene-3[57-59] and T-cell Ig and ITIM domain[60-63]; detailed information about the potential immune checkpoints involved in EC in Figure 1[63-66].

Regulatory T lymphocytes: Tregs are $CD4^+CD25^+Foxp3^+$ T cells that play an important role in suppressing the host immune response in the TME[67-70]. The infiltration of Tregs may be correlated with tumor invasion, progression, metastasis and poor survival after chemotherapy[68-71], and the infiltration of Tregs has also been shown to be negatively correlated with antitumor effector cells such as CTLs and NK cells in ESCC[72]. In addition, the hypomethylation-induced chemokine CCL20 in the TIME could affect the immune balance and promote the progression

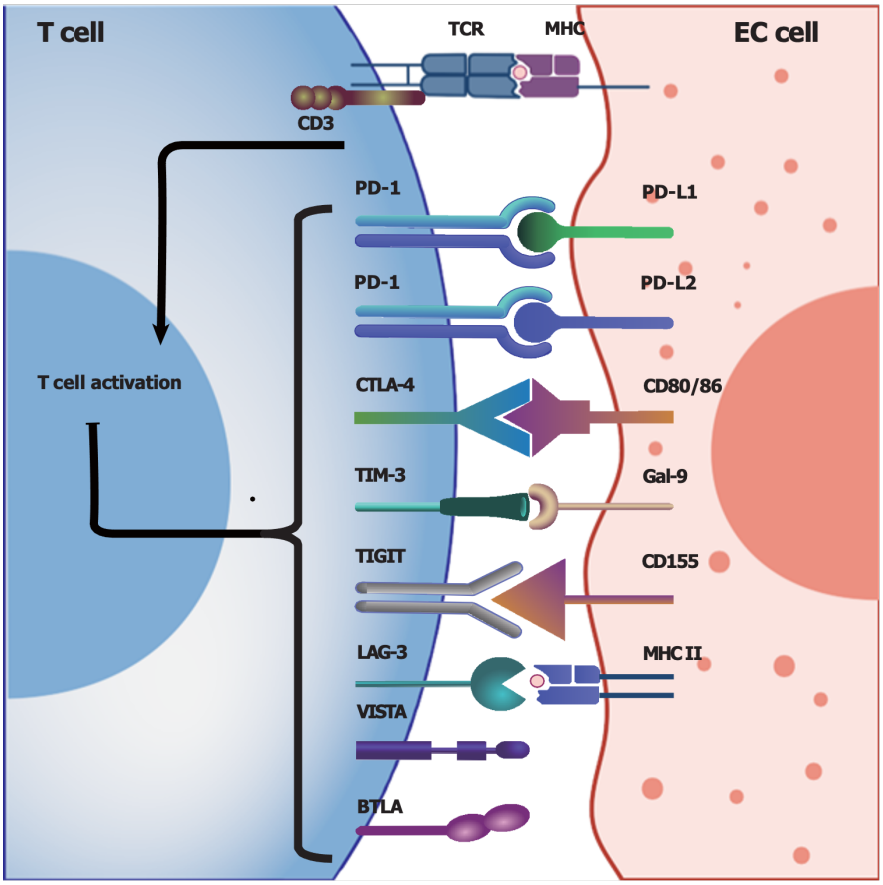

Figure 1 Summary of potentially involved immune checkpoints in esophageal cancer. T cells can be activated by interacting with major histocompatibility complexes expressed on esophageal cancer (EC) cells, and the presence and interaction of immune checkpoints with their ligands can suppress T-cell activation and function to achieve immunosuppression. Herein, we summarize the immune checkpoints and their ligands that are potentially involved in the tumor microenvironment of EC. Programmed cell death protein 1, cytolytic T lymphocyte-associated antigen-4, T-cell immunoglobulin and mucin-domain containing-3 (TIM-3), T-cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain (TIGIT), lymphocyte activation gene 3 (LAG-3), V-domain Ig suppressor of T-cell activation and B- and T-lymphocyte attenuator are expressed on T cells, while TIM-3, TIGIT and LAG-3 are also expressed on natural killer cells. EC: Esophageal cancer; TCR: T cell receptor; MHC: Major histocompatibility complex; CD: Cluster of differentiation; PD-1: Programmed cell death protein 1; PD-L1: Programmed cell death ligand 1; PD-L2: Programmed cell death ligand 2; CTLA-4: Cytolytic T lymphocyte-associated antigen-4; TIM-3: T-cell immunoglobulin and mucin-domain containing-3; Gal-9: Galectin-9; TIGIT: T-cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain; LAG-3: Lymphocyte activation gene 3; VISTA: V-domain Ig suppressor of T-cell activation; BTLA: B- and T-lymphocyte attenuator.

of EC, possibly contributing to the infiltration of Tregs in ESCC[73]. Moreover, Han *et al*[74] showed that Tregs may have the highest interleukin (IL)-32 expression in the TME of ESCC patients, and this expression is positively correlated with that of Foxp3, potentially promoting tumor progression; in addition, IL-32 may also induce interferon (IFN)-γ secretion by $CD8^+$ T cells and facilitate antitumor immunity. Additionally, an imbalance in Th17/Treg cells has also been reported to occur during the development of Barrett's esophagus, the precursor of EAC, through the regulation of the release of certain inflammatory cytokines[75].

Generally, T cells may experience functional loss or exhaustion in the TIME through interactions with various coinhibitory factors, and Tregs could play a crucial role in immunosuppression in the TME. Therefore, elucidating the functions and interactions of T cells with other cells in the TIME and understanding the mechanism of Treg-mediated tumor immune escape could provide valuable insights into the mechanisms of tumor immune escape, and thus further provide important evidence for novel immunotherapeutic strategies aimed at overcoming tumor immune escape.

NK lymphocytes

NK cells are another type of tumor cell-killing lymphocyte that has garnered significant attention in cancer immunotherapy[76]. Previous preclinical and clinical studies have shown promising results for NK cell-related immunotherapy, and provided a novel perspective on immunotherapeutic strategies for NK cell-related treatments[77]. However, NK cells often experience a reduction or exhaustion in the immunosuppressive TME similar to that of T cells, which may also limit their antitumor effects[76,78].

The number of NK cells has been shown to be significantly lower in ESCC tissues than in adjacent nontumor tissues; in addition, a specific subset of cells, NK-C3-KLRC1 has been shown to differentiate from NK-C1-NCR3, and the number of NK-C2-STMN1 cells was significantly increased in ESCC[22]. The NK-C1-NCR3 subset has been shown to express relatively high levels of NCR3, CD266, NKG7 and LAMP1, and the NK-C3-KLRC1 and NK-C2-STMN1 subsets have been

shown to express relatively high levels of KLRC1 and ITGA1[22]. As a cell surface receptor primarily expressed on NK cells and some types of T cells, NK group 2 member D (NKG2D) can interact with its ligands (NKG2DLs) to activate NK cells and T cells, and subsequently enhance immune surveillance and the clearance of tumor cells or infected cells[79,80]. Researchers have shown that the expression of NKG2DLs is significantly higher in ESCC tissues than in control tissues, and ESCC cells exhibit increased NKG2DL expression, thus providing a potential therapeutic target for ESCC *via* the use of NK cells[78]. Moreover, the inhibitory receptor NKG2A has been shown to be upregulated in NK cells in ESCC tissues compared to adjacent nontumor tissues[22], and a higher level of TIM-3 in tumor-infiltrating NK cells has been shown to be correlated with functional impairment and related to tumor invasion, lymph node metastasis and advanced stages in EC patients[56]. Notably, the expression of $CD16^{bright}CD56^{dim}$ may significantly decrease in NK cells in ESCC, leading to a weakened antibody-dependent cell-mediated cytotoxicity response mediated by cetuximab, which binds to the CD16 receptor on NK cells and targets the epidermal growth factor receptor (EGFR)[81,82].

Furthermore, numerous cytokines may also participate in regulating the immuno-activation of NK cells. For instance, transforming growth factor (TGF)-β partially contributes to the downregulation of CD16 expression on NK cells, resulting in impaired NK cell function[81]. A lack of IL-18 in ESCC tissues may induce the production of IFN-γ in NK cells and $CD8^+$ T cells, and potentially promote the clearance of tumor cells and improve the TME in patients with EC[83]. The expression level of IL-6, an important cytokine secreted by ESCC cells in the TME, has been shown to be higher in tumor tissues and blood circulation in ESCC patients, and may significantly upregulate the expression of CD39 on NK cells and impair the functions of NK cells, as well as be related to the poor prognosis of ESCC patients[84]. Another clinical study reported that IL-6 and IL-8 secreted by ESCC cells may downregulate the expression of certain activating receptors on NK cells and impair the function of NK cells by activating the signaling transducers and activators of transcription 3 (STAT3) signaling pathway[85]. Taken together, the above results demonstrate the decreased number and dysfunction of NK cells, effects that may disrupt immune surveillance in cancer patients, and pose a challenge for the investigation and clinical application of NK cell-related immunotherapy in ESCC patients.

Immune suppressive cells

Macrophages: Macrophages are important components of the innate immune system, and play pivotal roles in recognizing and removing damaged cells, pathogens and other foreign matter, as well as regulating adaptive immune responses by secreting various cytokines and chemokines[86]. Based on their functions and phenotypes, tumor-associated macrophages (TAMs) can be classified into two types: M1 and M2 macrophages[86,87]. M1 macrophages have proinflammatory properties and primarily participate in clearing pathogens, whereas M2 macrophages promote cell proliferation and tissue repair[86,87]. M1 macrophages in the tumor stroma are involved mainly in inhibiting the migration and invasion of ESCC cells, and serve as good prognostic factors for ESCC patients[88,89].

As an element of immunosuppression, M2 macrophages enriched in the TME of ESCC may suppress cell-mediated immune responses, secrete immunosuppressive factors and promote tumor angiogenesis[22]. M2 polarization may increase the expression of PD-L2 in ESCC cells, and lead to tumor immune escape and progression *via* PD-1-related signaling pathways[89]. In addition, Lu *et al*[90] reported that the upregulation of S100A7, a member of the S100 superfamily, could promote macrophage infiltration and M2 polarization, facilitating tumor angiogenesis by enhancing the activation of the p-ErK and p-FAK signaling pathways in the TME of ESCC. IL-32, which is highly secreted by Tregs, may promote the formation of an immunosuppressive TME; in addition, researchers have shown that IL-32, which is secreted from ESCC cells *via* extracellular vesicles, may shuttle into macrophages to promote M2 polarization *via* the FAK-STAT3 signaling pathway, further contributing to ESCC metastasis[91]. Moreover, Wang *et al*[92] reported that ESCC $FOXO1^+$ cells may promote M2 polarization and recruitment to the TME in ESCC through the transcriptional regulation of CCL20 and CSF-1, and $FOXO1^+$ tumor-induced M2 macrophages could promote tumor proliferation through FAK-PI3K-AKT signaling, which could be blocked by the blockade of PI3K[92]. In a rodent ESCC model, researchers found that CCL18, a chemokine secreted by TAMs, may promote tumor cell proliferation through the Janus-activated kinase 2 (JAK2)/STAT3 signaling pathway, and higher CCL18 levels are correlated with poor prognosis in ESCC patients[93]. To investigate the potential therapeutic efficacy of CCL18, researchers synthesized a CCL18-blocking peptide (Pep3) and found that it could inhibit the proliferation of EC-109 cells, suggesting potential targets through which CCL18 represses the progression of ESCC[93]. CCL22, another chemokine produced by TAMs in ESCC, may activate the FAK/AKT pathway and facilitate the malignant progression of ESCC cells[94]. Moreover, M2 macrophages may transmit the long noncoding RNA (lncRNA) AFAP1-AS1 to ESCC cells *via* secreted exosomes, downregulating miR-26a expression and upregulating ATF2 expression, thereby promoting tumor cell invasion and metastasis in EC[95]. Furthermore, a recent study showed that exosomes secreted by M2 macrophages carrying LINC01592 could be transferred to EC cells, resulting in a decrease in MHC-I expression, thereby allowing tumor cells to escape from attacks by $CD8^+$ CTLs[96]. When the E2F6/NBR1/MHC-I signaling pathway was disrupted by small interfering RNAs or corresponding blocking antibodies, the tumor-promoting effects induced by LINC01592, as well as M2-driven tumor growth, were significantly inhibited[96]. In summary, M2 macrophages play an inhibitory role in the TIME of EC and can be recognized as key regulators of cancer occurrence, progression and metastasis. Therefore, targeting M2 macrophages and related signaling pathways may provide a promising perspective on therapeutic strategies for EC management.

MDSCs: MDSCs are widely accepted as a population of immature bone marrow cells, that can be classified into granulocyte-like MDSCs (G-MDSCs) and monocyte-like MDSCs (M-MDSCs)[97]. Both G-MDSCs and M-MDSCs play important roles in inhibiting immune cell activities in the TME, thus promoting tumor growth and metastasis[97]. It has been reported that the proportions of MDSCs and Tregs are significantly greater in EC patients than in controls, further suggesting an immunosuppressive role of MDSCs in EC[98]. Therefore, inhibiting the recruitment of MDSCs to the TME might be a promising approach for treating EC *via* immunotherapy. For example, TGF-β secreted by MDSCs in the TME

may induce the phosphorylation of Smad2/Smad3, and contribute to the increased expression of the cancer/testis-associated gene *Maelstrom* (*MAEL*) in EC cells[99]. MAEL may be correlated with increased IL-8 expression by regulating the Akt1/RelA signaling pathway, and IL-8, in turn, may guide the recruitment of MDSCs into the TME of ESSCs[99]. In addition, the expression of MAEL in ESCC cells has been shown to be associated with recurrence and poor prognosis[99]. Moreover, it has been shown that the gene developmentally downregulated 9, which is critical for maintaining the stemness phenotype of ESCC cells, can regulate the expression of *CXCL8* through the ERK signaling pathway, thereby contributing to the recruitment of MDSCs to the TME[100].

In addition to focusing on the recruitment of MDSCs, inhibiting MDSC function in the TME might be another important strategy. MDSCs with higher CD38 expression have been shown to be better able to inhibit activated T cells and promote tumor growth than MDSCs with lower CD38 expression[101]. This enhanced immunosuppressive capacity of $CD38^{high}$ MDSCs may be attributed to their increased production of inducible nitric oxide synthase (iNOS), since the upregulated iNOS may act as an immunosuppressive molecule to suppress the immune responses of T cells and contribute to tumor immune escape[101]. Moreover, EC patients exhibit increased numbers of MDSCs and Th17 cells in the peripheral circulation, as well as increased levels of plasma Arg1 and iNOS mRNA in peripheral blood mononuclear cells[102]. Additionally, the expression of myeloid cell markers in ESCC may be positively correlated with the increased expression of certain immune checkpoints, such as PD1, TIM3 and V-domain Ig suppressor of T-cell activation, as well as the development of ESCC[103]. However, the depletion of $Gr1^+$ MDSCs may reduce the number of MDSCs, decrease the expression levels of immune checkpoint molecules, and inhibit tumor growth, suggesting the potential roles of MDSCs in the immunosuppression and progression of ESCC[103]. Furthermore, another fundamental study reported higher levels of lnc-17Rik in MDSCs derived from the peripheral blood of EC patients, and indicated that lnc-17Rik may enhance tumor immunosuppression by increasing the expression and enhancing the activation of certain key genes involved in MDSC differentiation, such as arginase 1, cyclooxygenase 2, NOS2, and NADPH oxidase 2[104]. These findings highlight the significance of elucidating the functions of MDSCs in the TIME, and suggest potential targets for therapeutic interventions aimed at overcoming immunosuppression and improving therapeutic efficacy in patients with EC.

TUMOR CELL-RELATED IMMUNOSUPPRESSIVE FACTORS

Although EC exhibits strong immune responsiveness, as previously mentioned, it may still achieve immune escape in the immunosuppressive TME through various mechanisms (Figure 2), including the downregulation of MHC expression, the secretion of immunosuppressive factors and alterations in tumor metabolism.

Downregulation of MHC expression

Tumor immune escape is often accompanied by a decrease in or loss of MHC molecules, which play crucial roles in the recognition and killing of tumor cells by immune cells[105]. Notably, the expression of HLA-ABC molecules is usually decreased or even absent in ESSC tissues[106]. Specifically, a previous study reported that approximately 41% of EC patients had no HLA-ABC expression, more than half of the EC patients had weak expression, and only approximately 3% of the EC patients had strong HLA-ABC expression[106]. In addition, the reduced or absent expression of HLA-ABC in ESCC may be strongly correlated with the expression of certain molecules that participate in antigen processing, such as b2m, ATP binding cassette subfamily B member 1 (TAP1), TAP2, LMP2 and LMP7[107]. Moreover, allelic loss in the 6p21.3 region, observed in approximately 46.9% of ESCC patients in a Chinese study, has been shown to be associated with the downregulation of HLA class I antigens[108,109], and DNA hypermethylation may result in deficient expression of HLA class I genes in ESCC[110]. Numerous ncRNAs, such as miR-125a-5p and miR-148a-3p, may downregulate the expression of TAP2 and HLA-I to affect the antigen presentation process[111], and exosomal LINC01592 released from TAMs may also downregulate the expression of MHC-I in EC cells and promote malignant EC progression[96]. Downregulation of the expression of MHC molecules in the TME hampers antigen processing and presentation processes, thereby enabling tumor immune evasion in patients with EC. Investigating these underlying mechanisms is crucial for advancing innovative cancer immunotherapy focused on these molecules.

Secretion of immunosuppressive factors

An immunosuppressive TME is partially generated by immunosuppressive factors secreted by tumor cells, immune cells and stromal cells[112], and these factors play crucial roles in tumor proliferation, angiogenesis and invasion, as well as in EC progression[113]. Some classic immunosuppressive cytokines, such as TGF-β and IFN-γ, may inhibit the functions of immune cells, thereby weakening the ability of the immune system to attack tumor cells[113,114].

The TGF-β signaling pathway could play a dual role in cancer development depending on the stage of disease[114]. Under pathological conditions, the overexpression of TGF-β may lead to epithelial mesenchymal transition, extracellular matrix deposition and the formation of cancer-associated fibroblasts, resulting in fibrotic diseases and cancers[115]. In addition, TGF-β can restrict the infiltration of T cells to the TME and decrease antitumor immunoactivity[116]. Moreover, TGF-β derived from MDSCs in the TME of ESCC may increase PD-1 expression in $CD8^+$ T cells, leading to resistance to immunotherapy *via* PD-1/PD-L1[27]. Furthermore, the combination of TGF-β and PD-L1 blockade has been shown to significantly increase the number of tumor-infiltrating T cells and reduce the tumor burden in EAC patients[116].

The IFN signaling pathway also plays a dual role in the TME. On the one hand, IFN-γ acts as a cytotoxic cytokine and induces tumor cell apoptosis, thus exerting antitumor effects[117]. On the other hand, IFN-γ may contribute to immunosuppression in the TIME by promoting the synthesis of immune checkpoint-related factors, such as PD-L1, thus

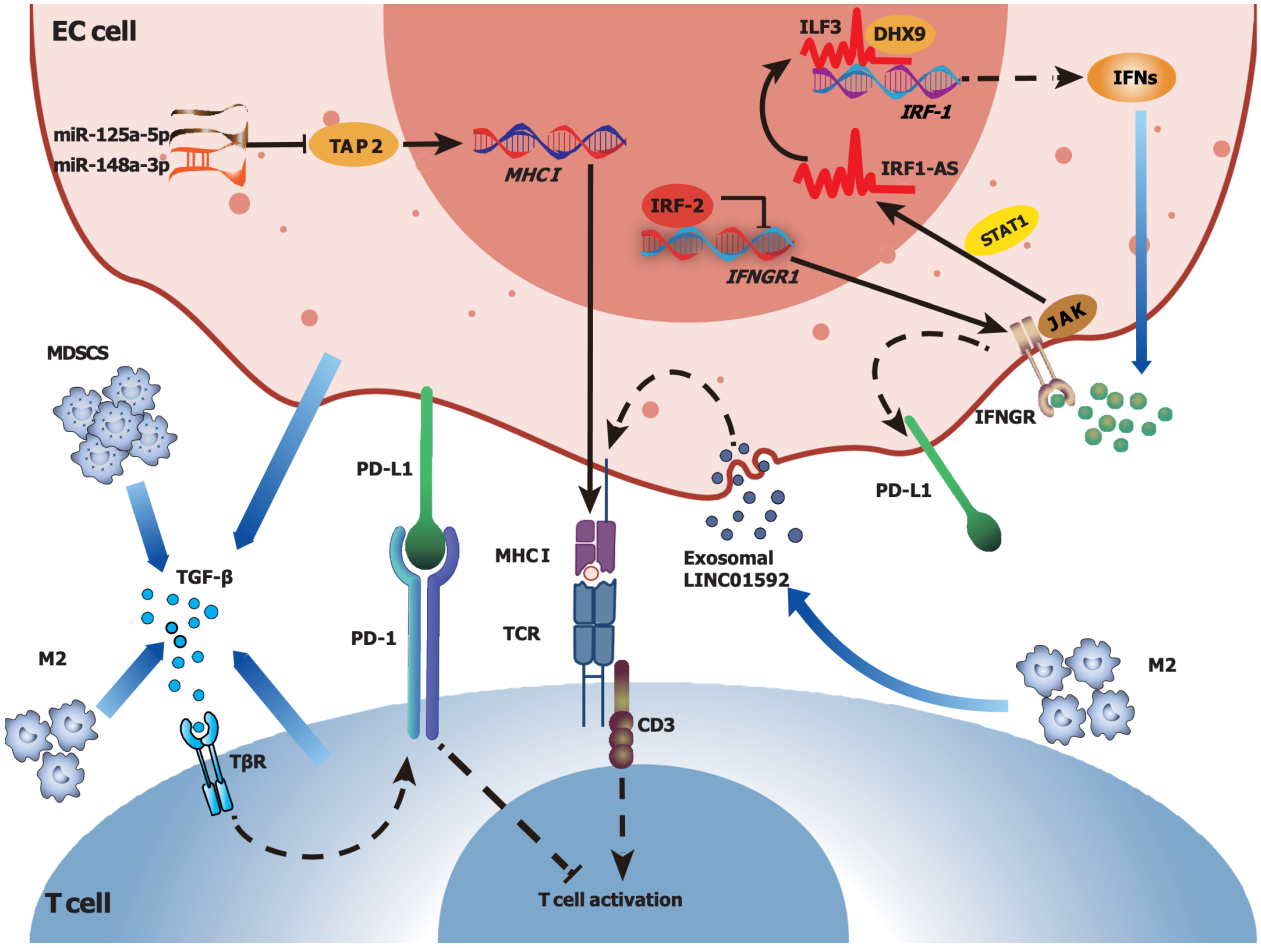

Figure 2 Potential mechanisms of tumor immunosuppressive microenvironment formation in esophageal cancer: Major histocompatibility complex downregulation and immunosuppressive factors. In esophageal cancer (EC) cells, miR-125a-5p and miR-148a-3p may downregulate ATP binding cassette subfamily B member 2 translation and major histocompatibility complex (MHC)-I expression, and exosomal LINC01592 released by M2 macrophages may also downregulate MHC-I expression. Transforming growth factor beta secreted by various cells can enhance programmed cell death protein 1 expression on T cells, and interferon (IFN)-γ can upregulate programmed cell death ligand 1 expression on EC cells, subsequently contributing to immunosuppression in the tumor microenvironment. Additionally, EC cells may acquire immune resistance by downregulating the expression of IFN-γ receptors and suppressing the activation of Janus-activated kinase signaling. EC: Esophageal cancer; TCR: T-cell receptor; MHC: Major histocompatibility complex; PD-1: Programmed cell death protein 1; PD-L1: Programmed cell death ligand 1; MDSC: Myeloid-derived suppressor cell; M2: Type 2 macrophage/suppressive macrophage; TGF-β: Transforming growth factor beta; TβR: Transforming growth factor beta receptor; IFN: Interferon; IFNGR: Interferon gamma receptor; IRF-1: Interferon regulatory factor 1; IRF-2: Interferon regulatory factor 2; IRF1-AS: Interferon regulatory factor 1 antisense RNA; ILF3: Interleukin enhancer binding factor 3; DHX9: DExH-box helicase 9; STAT1: Signal transducer and activator of transcription 1; JAK: Janus-activated kinase; TAP2: ATP binding cassette subfamily B member 2.

allowing tumors to escape immune surveillance[117,118]. Notably, interferon regulatory factors (IRFs) play important roles in regulating the effects of IFN-γ: IRF-1 is generally considered a tumor suppressor, whereas IRF-2 is regarded as an oncogenic factor[119,120]. In addition, IRF-1 expression has been shown to be decreased, and IRF-2 expression has been shown to be increased in EC, contributing to the suppression of immune responses[121]. Most importantly, IFN-γ can interact with various factors. For instance, an IFN-induced lncRNA, IRF1-AS, has been shown to activate IRF-1 transcription by interacting with IL enhancer binding factor 3 and DExH-box helicase 9, thereby activating the IFN response[119]. However, IRF-2 may inhibit the transcription of IFN-γ receptor 1 (*IFNGR1*) by binding to specific motifs in the *IFNGR1* promoter, thereby reducing the sensitivity of EC cells to IFN-γ and enhancing the resistance of EC cells to IFN-γ[120]. IFNs can regulate the JAK-STAT signaling pathway, and the activation of STATs often facilitates tumor progression[122,123]. MAGE-C3 may enhance the interaction between IFNGR1 and STAT1 by binding to IFNGR1, which can activate IFN-γ signaling and upregulate PD-L1 expression, thus contributing to immunosuppression[118]. Moreover, the overexpression of MAGE-C3 may be associated with lymph node metastasis and poor survival in ESCC patients[118]. Therefore, various factors have been suggested to participate in the immunosuppression mediated by IFN-γ in EC, but the underlying mechanisms urgently need to be elucidated.

The interplay of cytokines and signaling pathways in the TIME of EC results in the construction of a complex network, and certain key cytokines, such as TGF-β and IFN-γ, play dual roles in tumor progression by promoting tumor growth and immune escape or exerting antitumor effects. Understanding the intricate interactions among these factors might provide insights into potential therapeutic targets for enhancing antitumor immunity in patients with EC. Further research is warranted to explore novel strategies for immune modulation and improving immunotherapeutic efficacy in

EC patients.

Tumor metabolism

Tumor metabolism is usually characterized by high heterogeneity and constant remodeling due to the evolution of cancer cells, and metabolic reprogramming is a distinctive feature of malignant tumors[124]. The dynamic interactions among tumor cells and various immune cells could lead to metabolic competition within the tumor ecosystem, limiting the availability of nutrients for immune cells and resulting in acidification of the TME, thereby impairing the functions of immune cells[125]. In a previous study, ESCC patients were divided into high- and low-risk subtypes based on three genes associated with tumor metabolism, namely, *CD38*, *INPP5E* and *POLR3G*, and the high-risk subgroup exhibited decreased *CD38* and *POLR3G* expression and increased *INPP5E* expression[126]. Compared with patients in the low-risk subgroup, patients in the high-risk subgroup had increased Treg infiltration and decreased plasma cell infiltration in the TME, as well as significant metabolic differences in ESCC tissues[126]. Notably, ESCC was primarily associated with glycolysis, and EAC was strongly correlated with oxidative metabolism, glycolipid metabolism and the tricarboxylic acid cycle[127].

Under normoxic conditions, most tumors preferentially rely on glycolysis for energy, which is considered an advantage for survival and is known as the Warburg effect[128]. A recent study highlighted the inhibitory role of estrogen-related receptor gamma in the occurrence, proliferation and glycolytic activity of ESCC cells, and one of its specific agonists, DY131, could inhibit the proliferation and glycolytic activity of ESCC cells by modulating certain specific genes involved in the glycolytic pathway[128]. In addition, the combination of DY131 with PD-1 blockade may have a synergistic effect on the suppression of ESCC growth[128]. As a byproduct of glycolysis, lactate may play an important regulatory role in the development and progression of ESCC, and is closely correlated with immunosuppression in the TME[129]. Furthermore, intracellular hypoxia is also associated with the progression, treatment resistance and poor prognosis of various malignancies. Numerous genes associated with hypoxia, such as *PGK1*, *PGM1* and *SLC2A3*, have been shown to be correlated with poor prognosis in EAC patients; *EGFR* and *ATF3* may be correlated with poor prognosis in ESCC patients[130]. In addition, EAC patients with higher *PGK1* and *SLC2A3* expression and lower *PGM1* expression, and ESCC patients with higher *ATF3* expression and lower *EGFR* expression, may have increased infiltration of immunosuppression-associated cells, including memory-activated $CD4^+$ T cells, activated mast cells and M2 mac-rophages[130]. Furthermore, another clinical study focused on the co-expression of hypoxia-related genes and lncRNAs in digestive system pancancer, and identified 18 hypoxia-related lncRNAs (HRlncRNAs); patients with six of these identified lncRNAs (LUCAT1, MIR4435-2HG, LINC01711, AP000695.2, ADAMTS9-AS2, and AC087521.1) had increased infiltration of immune cells, such as B cells, cancer-associated fibroblasts, endothelial cells, monocytes, macrophages and bone marrow dendritic cells, in tumors, as well as a poor prognosis[131].

Certain metabolic pathways other than the glycolysis and hypoxia pathways are also involved in EC. Zhao *et al*[132] identified six genes associated with iron metabolism and iron death (*PRNP*, *SLC3A2*, *SLC39A8*, *SLC39A14*, *ATP6V0A1*, and *LCN2*) in ESCC, and these genes may be associated with the infiltration of immune cells, tumor mutational load and ESCC prognosis. In addition, lncRNAs such as LINC01068, TMEM92-AS1 and AC243967.2 have been reported to be correlated with iron metabolism and iron death, and be closely related to the infiltration of immune cells in ESCC[133]. Moreover, Zhang *et al*[134] reported that mitochondrial energy metabolism is associated with the TIME and poor prognosis in ESCC patients, and identified several fatty acid metabolism-related genes that are predictors of EC prognosis [135]. Additionally, tryptophan-derived metabolites have been shown to contribute to tumor immune escape, and been identified as biomarkers for EC metastasis and prognosis[136].

These insights emphasize the importance of metabolic alterations in the TME of patients with EC. Understanding the intricate metabolic interactions between tumor cells and immune cells could guide the development of targeted therapies for different subtypes of EC, and further research in these areas may open new avenues for the management of patients with EC.

CONCLUSION

In this review, we mainly described the potential mechanisms of immunosuppression in the TME of patients with EC, which opens up an interesting and promising field of future immunotherapies. The presence of decreased immune cells and increased immunosuppressive cells, including exhausted $CD8^+$ T cells and NK cells, Tregs, M2 macrophages and MDSCs, in the TIME of EC is not rare, and these cells may contribute to tumor immune escape and tumor progression. Moreover, various other factors related to tumor cells also participate in the formation of an immunosuppressive microenvironment in EC, such as the downregulated expression of MHC molecules on tumor cells, the release of immunosuppressive cytokines by tumor cells and their surroundings, and altered tumor metabolism. With a deeper and more comprehensive understanding of the complexity and heterogeneity of the TME, such as tumor types, the distribution and function of infiltrating immune and nonimmune cell subsets, the expression of cytokines and the activation or inhibition of signaling pathways in the TME, we may better elucidate the mechanisms of the immunosuppressive microenvironment, better understand the differences in patient response to the same immunotherapeutic strategies, and accurately predict the efficacy of immunotherapeutic approaches; thus, personalized treatments can be developed to overcome the effects of immune suppressive factors, improve the efficacy of immunotherapy, and maximize the advantages of immunotherapy.

FOOTNOTES

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