Review article

Research Progress on Tumor Immune Escape

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ABSTRACT Accumulating evidences indicate that tumor cells could escape the monitoring of the human immune system through variety ways, such as the tumor induced decrescence of antigen-presenting, up-regulation of immunosuppressive factors and supplement the amount of regulating cells which participate into the immune suppressive networks including regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and distinct subsets of immature and mature special regulatory dendritic cells (DCs). Moreover, the activation of negative costimulatory signals and counterattack strategies of Fas system were basic means of tumor cells escape immune destruction.

Key Words: Tumor immune escape; Immunosuppressive factors; Immune regulatory cell; Negative costimulatory signals; Fas/FasL counterattack

Tumor escape is a major obstacle to successful immunotherapy. A good understanding about the relationship between the cancer and human immune system and the diversity of the tumor immune escape mechanisms will produce a new positive impact on tumor immunotherapy strategies. To promulgate the recent research progress on the tumor immune escape, and explore the method of tumor immunotherapy, as well as the theory of guiding researches and clinical applications, papers published in recent years were widely studied and reviewed. Tumor cells could escape the immune response monitor through variety ways are described as follow, including the decrescence of tumor-induced antigen presenting, the up-regulation of immunosuppressive factors, increase or supplement the number of regulatory cells and the activation of negative costimulatory signals etc.

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1.The transformation of antigen–presenting mechanism

In order to escape immune recognition, tumor cells take different mechanisms, including modification, reduction or complete loss of its cell surface antigens. For instance, the malignant melanoma cell lines could produce a soluble protein that diminishes the expression of the gene encoding the melanocyte lineage Melan-A/MART-1 antigen through down-modulation of its promoter to make the tumor tissues to escape the recognition of specific T cells [1]. Like viruses, tumor cells could also undergo “antigenic drift” that make the tumor cell surface antigens cannot be recognized by specific cytotoxic T lymphocytes (CTLs) any longer through the accumulation of point mutations. The endogenous (class-I) antigen presentation machinery (APM) plays a crucial role in the generation of peptides from endogenously synthesized proteins，like tumor antigens, and in their presentation to CTLs. Several defections of APM elements, including the transporter associated with antigen processing (TAP) and components of the immunoproteosome (LMP-2, LMP-7) have been found in the tumors of head and neck, bladder carcinoma and brain astrocytic glioma, which supports that APM alterations, in some extent, have caused tumor cells to tolerate the immune response [2].

By blocking CTL signals, tumor cells could be tolerant to CTL

through losing or changing the expression of human leukocyte class I antigen (HLA-I) to induce the abnormity of tumor antigen-presenting. Researches about the tumor cells in metastatic tissues revealed a new mechanism of antigen's lack expression in tumor cells. It was reported that there are two cell types in metastatic lesions with different characteristics: one is sensitivity for immunotherapy, appearing up-regulated HLA-I expression; another one is tolerant to immunotherapy with low level of HLA-I which presumably is owning to the irreversible defects in tumor cell structure (hard lesions) that make it fail to up-regulate HLA-I and irresponsible to the immune stimulations, and the nature of the preexisting HLA-I lesion in the cancer cell has a crucial impact determining the final outcome of cancer immunotherapy[3,4]. Moreover, the soluble molecule of HLA-I (sHLA-I) has also been concerned which is the different and a secreted extracellular soluble form in the protein expression-processing produced by abnormal cropping. By secreting sHLA, tumor cells could inhibit the activity of NK cells and induce tumor antigen-specific T cells apoptosis. However, synthetic sHLA-I could cause gastric cancer cell growth inhibition and apoptosis[5], which indicates that sHLA-I might be used as a novel type of tumor immunotherapy drugs, but its mechanism needs further study due to its inhibitory effect on immune system.

2. Immunosuppressive factors

2.1 Galectin

Galectin participates in various physiological and pathological processes of tumor growth and metastasis. Galectin-1 could induce T cell apoptosis and the secretion of immunosuppressive factors that have inhibition or delay function on T cell effect. According to substantial evidence galectin-1 exists in multiple different types of tumors, including astrocytoma, melanoma and colon cancer. The expression of galectin-1 in tumor associated stromal tissues has close association with the different clinical pathological parameters, including tumor invasiveness and lymph node metastasis.

Rubinstein et al.[6] found that cancer could produce micro-environment of immune suppression and anti-inflammatory possibly through the expression of galection-1. It had observed that a significant reduction in the number of tumor cells and enhancement of tumor-specific T cell signal when galectin-1 expression was blocked, and galectin-1 influences antitumor immune through regulating CD4+ and CD8+ T cell growth and immune function. In the other study, galectin-1 might regulate growth and metastasis of glioma. It should be special stressed that the expression level of galectin-1 in tumor cells increases after ionizing radiation treatments, which suggested that to avoid other unpredictable stimulations, inhibiting of galectin-1 expression should be considered when cancer patients accept radiation therapy[7]. Furthermore, the phenomenon of a high galectin-1 expression level together with a sensitivity of transforming growth factor β (TGP-β) was found in two kinds of mammary adenocarcinoma cell lines and one kind of lung cancer cell lines, which prompts that TGP-β might be activate Smad dependent pathway to control expression of galectin-1, and indicates that different immunosuppressive factors have interaction in regulation tumor immune escape [8].

2.2 Gangliosides

Gangliosides are acidic glycosphingolipids existing at the cell surface in different structures as clusters form which shape lipid rafts structure. Gangliosides have been found increased expression in many tumor cells, including GM1,GM2,GM3 and GD3, etc, and could inhibit number of steps in cellular immune signals, including the generation and presentation of antigen, T cell proliferation and cytokines such as interferon-γ（IFN-γ） production. Biswas et al. found that gangliosides produced by the human renal cell carcinoma (RCC) have effect on T cell apoptosis that could partially be inhibited by anti-GM2 antibody, and the gangliosides isolated from the surface of some patients RCC could inhibit TH1（IFN-γ）and TH2（IL-10）cytokine signaling [9]. However, gangliosides obtained from other types of tumor only inhibit the TH1 cells mediated immune signals. Therefore, antitumor immunity signals in cancer patients has partly influenced by tumor origin gangliosides at least.

The extracellular administration of purified gangliosides could inhibit the activation signal induced by monocytes and the production of pro-inflammatory factors mediated by Toll-like receptors (TLR), and significantly up-regulate the expression of interleukin-1(IL-1) receptor associated kinase M(IRAK-M) in monocytes. Gangliosides treatment could produce tolerance state of TLR signal transduction and lead to inactivation of innate immune signals, and the inhibition of TLR signaling activation could be reversed by gangliosides elution, which might be the partial mechanism of the gangliosides suppression on immune signal. In the tumor microenvironment, tumor cells could also guide to immune tolerance through gathering the APC cell membrane gangliosides to ignore the normal TLR signaling [10]. Recent studies have also found that cancer stem cell surface antigen CD133 contains a domain that could able to combine with ganglioside's domain in selective manner at GM1 and GD3, which could regulate the early period growth of tumor cells through cell-cell contact way[11]. Other immunosuppressive

factors also include TGF-β, IL-10, indoleamine 2,3-dioxygenase (IDO) and PGE- 2 etc.

3.Immunoregulatory cells

3.1 Regulatory T cells

The CD25+ T cells, being defined as regulatory T cells （Tregs）, have widely negative regulations on immune response. CD4+ CD25+ Foxp3 Tregs (a natural occurring T cell subset) could secrete selective cytokines to regulate the tumor microenvironment, and secrete soluble non-protein-like factors to interact with soluble factors such as arginase or IDO which has emerged as an important driver of immune escape in a growing number of cancers and cancer-associated chronic infections, resulting in a productive depletion of amino acid or NO, to inhibit γδ T cell proliferation and evading immune cells attack. In additions, it could inhibit the expression of TNF-related apoptosis-including ligand (TRAIL) on tumor infiltrating dendritic cells (TIDCs) induced by Bacillus Calmette vaccine (BCG), and thus inhibit the tumor cells apoptosis induced by TIDCs via TRAIL. CD8+ CD25+ Foxp3 Tregs being of strong immunosuppressive properties identified in colorectal cancer tissue showed inhibition effect on Th1 cytokine production and CD4+ CD25 T cell proliferation when it was synergistic induced by IL-6 and TGF-β1 in vitro. So, Tregs is one of the most critical mechanisms of tumorimmune escape and a major hurdle for successful tumor immunotherapy [12-14]. In addition, The proinflammatory IL-17–producing CD8+ T cells (Tc17 cells) are accumulated in human hepatocellular carcinomas (HCC) and enriched predominantly in invading tumor edge, where they promote disease progression by fostering angiogenesis, and the tumor-activated monocytes secreted a set of key cytokines (IL-1β, IL-6, and IL-23) to trigger the proliferation of Tc17 cells. These data revealed an intriguing mechanism in which human Tc17 cells are generated by a fine-tuned collaborative action between different types of immune cells in distinct tumor microenvironments [15].

Tumor cells could inhibit antitumor immunity effectively through the differentiation, amplification or recruitment of Tregs. Recently, a distinct set of chemokines that drive the recruitment of Tregs had been identified, namely thymus and activation-regulated chemokine (TARC or CCL-17) and macrophage-derived chemoattractant (MDC or CCL-22), whose receptors are both chemokines with affinity for the receptor CCR4 expressed on Tregs[16]. Compared with normal individuals, high level Tregs expression was found in a variety of cancer patients' peripheral blood and which had a closely relationship with them prognosis. However, there is an exception in colon cancer patients that high level expression of Tregs in normal colon mucosa presented poor prognosis and those in tumor tissues with their prognosis appears better[17]. Similarly, Tregs in tumor focus in endometrial cancer sufferers also had a lower level than normal human, and the mechanism need to be further investigated. In addition, though Tregs have been involved in the immunomodulation of immune responses and contribute to the patients with head and neck squamous cell carcinoma (HNSCC) progression and immune escape, the data of Schott AK et al not only indicated a significantly high increased abundance of CD4+ CD25(high) CD127(low) Tregs in the peripheral blood of patients with HNSCC, which in addition showed modulated expression levels of various functional proteins, and increased levels of chemokine CCL-22, which mediates migration of Tregs to the tumor and upregulation of the corresponding receptor protein CCR4 were observed in HNSCC, but also surprisingly showed that increased Treg levels were found even in patients with no active disease several years after tumor resection, with no significant correlation to the individual tumor stage, which suggested that HNSCC leads to a permanent shift of Treg levels with hardly recognizable recovery rates [18].

3.2 Dendritic cell

Dendritic cells (DCs) are extremely important for the generation and maintenance of antitumor immune signals. DCs differentiation obstacle or immature DCs increase is one of the important factors in tumor immune escape，which occurs in patients with various type of tumors, together with a declined ability of their peripheral blood mononuclear cells differentiation into DCs, and DCs surface receptors are lowly expressed, such as HLA-ABC, HLA-DR, CD86, intercellular adhesion molecule-1 (ICAM-1) and tumor necrosis factor receptor Ⅱ (TNFR Ⅱ) and so on[19, 20]. Observations of Kuang et al indicated that tumor microenvironments, including hyaluronan fragments derived from cancer cells, educate DCs to adopt a semimature phenotype, which in turn aids tumor immune escape by causing defects in the CD3/TCR complex and deletion of T cells, and tumors can educate DCs to differentiate into a regulatory DC subset, which contributes to constitution of the immunosuppressive tumor microenvironment and promotes tumor immune escape [21, 22]. It has been widely studied and applied that using combined immunotherapy to activate DCs producing antitumor signals. For example, the immunotherapy of DCs combined with granulocyte-macrophage colony-stimulating factor (GM-CSF) gene transferred tumor cells has showed 50% cure rate in tumor-bearing mice, and the cured mice have immune rejection for the re-transplanted tumor, which suggests that the memory of immune signals exist in

the mice. All the mice induced by combined immunotherapy have increased their cytotoxic immune signals, and the cured mice appeared stronger expression of IFN-γ induced by CD4 + T cells [23].

Death receptor 6 (DR 6), a member of tumor necrosis factor receptor superfamily which have been found expressed in plenty of tumor cell surface, could be cut off from the surface of tumor cells by tumor-associated matrix metalloproteinase-14 (MMP14) and released into the tumor microenvironment to suppress immune response. If mononuclear cells existed in the extracellular matrix with DR6, more than 50% monocytes which would differentiate into DCs would die. It shows that the combined action of DR6 and MMP14 which influences the production of antigen presenting cells (APCs) might be one of the mechanisms for tumor to evade the immune surveillance [24].

3.3myeloid–derived suppressor cells

Myeloid-derived suppressor cells (MDSCs) are a class of heterogeneous bone marrow cells, including immature macrophages, granulocytes, DCs and other bone marrow cells in early differentiation stage, which specifically express cell surface antigen CD11b and Gr-1. The most important way of MDSCs assisting tumors escape immune destruction is that MDSCs could secrete arginase to the tumor tissues which induces arginine depletion around TIDC to curb the T cell functions. MDSCs also could produce large amounts of inflammatory cytokines and chemokines, that might be one of the reasons for producing cachexia in cancer patients. Researches on MDSCs aggregation mechanism in cancer patients have revealed that one marrow-related protein S100A9 could promote MDSCs production in tumor bearing mice, and might be one of the potential molecular mechanisms of MDSCs accumulation in tumor. It showed that the mice with S100A9 deficiency could produce effective antitumor immune signals and rejection of tumor inoculation, with the over expression of S100A9 could inhibit the maturation of DCs and macrophages and induce the aggregation of MDSCs [25].

MDSCs also play an important role in the process of inflammation developing to cancer. In the study using 4T1 mouse breast cancer cells and IL-1 receptor (interleukin-1 receptor, IL-1R)-deficient mice, Bunt et al. found that IL-1 could induce the aggregation of MDSCs, inhibit antitumor immunity, and promote tumor development, and IL-6, as a regulator of IL-1, could reverse MDSCs aggregation aroused by IL-1. IL-1b activates MDSCs in vivo and in vitro by IL-1RI/NF-kappa B path way, and it could be inhibited by blocking IL-1 receptor signaling [26, 27]. MDSCs could affect the antitumor immunity by interacting with other immune cells yet. For instance, MDSCs inhibit T cells and natural killer cells (NK cells) function in vivo and in vitro, including the cytotoxicity as well as the expression of NK cell receptor NKG2D and IFN-γ. MDSCs membrane-bound TGF-β1 might be involved in the inhibition of NK cells, and the functional impaired NK cells in the liver of mice with carcinoma in situ could be recovered its function by reducing the amount of MDSCs [28]. The interaction between MDSCs and macrophages, which promotes MDSCs producing IL-10 and inhibits macrophage producing IL-12, could inhibit antitumor immunity by cell contaction. This inhibition could be reversed by chemotherapeutic drug gemcitabine by inhibiting IL-10 production and activating effective T cell immune signals [29].

MDSCs are not always show the characteristics of antitumor immune suppression, for some MDSCs have the function of APC through induction, which could be used as cell vaccine for cancer immune therapy. Transformed MDSCs, which have shown the tumor antigen presenting function and the characteristics of α-galactosidase nerve-acylamino, the ligand of natural killer T cells (NKT), and could significantly prolong the tumor-bearing mice life. In addition, Stimulated by activated NKT cells, the phenotype or mature signs of MDSCs, including expression of CD11b, CD11c, and CD86, are all changed [30].

4. Negative regulatory pathway

4.1 Cytotoxic T lymphocyte associated antigen –4

Evidences indicated that co-stimulatory molecules which have negative regulating function are widely expressed on the surface of tumor cells, effective T cells and Trges. One of the best-studied regulatory signals is mediated by CTL associated antigen-4 (CTLA-4, CD152), a ligand of B7 expressed on activated T cells and naturally occurring Tregs. CTLA-4 signal transduction delay would increase antitumor signals, and antibody mediated blockade of CTLA-4 might be one of the most common immunotherapy that have been applied to treat a variety of malignant tumors, enhancing antitumor response and inducing tumor recession in a variety of tumor patients such as advanced melanoma [31, 32].

Although, there are still a number of side effects known as immune-related adverse events (IRAEs) in the clinical application. A plenty of cancer patients have autoimmune toxicity after anti-CTLA-4 treatment in which the most common one is enterocolitis that could be cured by corticosteroids. Researches on bladder cancer patients accepted anti-CTLA-4 treatment showed that the Th1 cytokine IFN-γ is highly expressed, while Th2 cytokine IL-10 highly expressed before treatment is down regulated, which is consistent with the adverse events. IL-10 reduction might be one of the reasons of "adverse events" after the anti-CTLA-4

treatment, but the mechanism still needs further studies[33]. The side effects caused by Anti-CTLA-4 antibody increased the complexity of immune therapy. Hodi et al. have shown the study that periodic infusions of anti-CTLA-4 antibodies after vaccination with irradiated, autologous tumor cells engineered to secrete GM-CSF (GVAX) generate clinically meaningful antitumor immunity without grade 3 or 4 toxicity in a majority of metastatic melanoma patients[34]. This provides a solution for the side effects caused by anti-CTLA-4 antibody treatment.

4.2programmed death−1

The interaction of programmed death-1 (PD-1, CD279) and its ligand-1 (PD-L1, CD274, known as B7-H1) widely expressed in cancers might also lead to immune suppressive microenvironment in tumor. Constitutive or inducible expression of B7-H1 confers resistance to therapeutic anti-CD137 antibody in mice with established tumors. The resistance is accompanied with failure of antigen-specific CD8+ CTLs to destroy tumor cells without impairment of CTL function. Blockade of B7-H1 or PD-1 by specific monoclonal antibodies could reverse this resistance and profoundly enhance therapeutic efficacy. Our findings support that B7-H1/PD-1 forms a molecular shield to prevent destruction by CTLs and implicate new approaches for immunotherapy of human cancers[35]. B7-H1 binding to inducible inhibitory receptor PD-1 in activated T cells could initiate the phosphorylation of immunoreceptor tyrosinebased inhibitory motif (ITIM) to promote apoptosis of antigen-specific human T cell clones in vivo and in vitro[36]. The expression of B7-H1 is closely related not only with pathological grade, clinical stage and recurrence index, but also with clinical pathologic diversity, including the invasion, lymph node metastasis and distant tissue transfer, that could be used as potential prognostic indicators in clinical treatment.

It has been revealed that activation of TLR4 signaling pathways could increase B7-H1 expression in bladder cancer cells. This regulation would be decreased by blocking ERK or JNK signaling pathways[37]. The appearance of positive tumors accompanied with increasing tumor-infiltrating Tregs points out that B7-H1 might down regulate the antitumor immune signals by regulating CD4+ CD25+ Foxp3 Tregs. In the 1D8 mouse model of ovarian carcinoma, the expression of B7-H1 on its MDSC suppresses antigen-specific immunity via interaction with PD-1 on Tregs. The level of B7-H1, PD-1 and CTLA4, which are highly expressed on Gr-1+ CD11b+ MDSCs obtained from both ascites and spleens of tumor-bearing mice, could not be detected on those cells from naive mice which do not suppress the antigen-specific immune, and Gr-1+ CD11b+ cells from naive mice could be induced to express B7-H1 by co-culture with 1D8 ovarian carcinoma cells. siRNA-mediated knockdown of B7-H1 in Gr-1+CD11b+ cells of 1D8 tumor-bearing mice alleviates suppression of antigen-specific immune responses, and antibody blockade of either B7-H1 or PD-1 retarded the growth of 1D8 tumor in mice. Therefore, blocking B7-H1 or PD-1 mediated immune suppressive signal could be used as a complement pathway for enhancing tumor specific T cell immune signal in cancer immunotherapy [38].

5. Fas / FasL counterattack and sFasL shield

Fas-dependent apoptotic pathway is regulated by the homologous interaction between the Fas receptor (CD95) and its ligand FasL (CD95L). In normal, the activated T lymphocytes could kill tumor cells by out-secrete FasL which interacts with the death receptor Fas on tumor cells to initiate the apoptosis of tumor cells, and dendritic and lymphoid 'exosomes' regulate immune activation, however, a variety of solid tumors could express FasL, and they also could release membranous materials mimicking these 'exosomes,' containing tumour antigens, FasL and other inhibitors for T cell activating signals abnormally expressed by tumor cells to make tumor cells to be of the capacity of transmitting death signals to the Fas positive effective T cells resulting in apoptosis and depletion of activated T cells and enhance the metastasis of tumor cells, and even the FasL positive tumor cells could kill the Fas positive T cells in vitro, for instance, the microbubbles on the surface of malignant melanoma cells could induce FasL-mediated T cell apoptosis, multiply showing the great capacity of FasL expression of tumor cells [39, 40]. On the other hand, Lyan et al. showed that FasL expression in CMT93 colon carcinoma cells down-regulated following stable transfection with a plasmid encoding antisense FasL cDNA could significantly reduce tumor development in syngeneic immunocompetent mice in vivo, and the tumor size was also significantly decreased with increased lymphocyte infiltration, though down-regulation of FasL expression had no effect on tumor growth in vitro. Thus, down-regulation of FasL expression by colon tumor cells results in an improved antitumor immune challenge in vivo, providing functional evidence in favor of the “Fas counterattack” as a mechanism of tumor immune evasion, and down regulating the FasL expression of tumor cells might be a new chance for antitumor immunotherapy [41].

Furthermore, though some tumor cells express Fas, they could still escape FasL-mediated apoptosis issued by T cells, which could not be ascribed to tumor counterattack against T cells or general resistance of the tumors to apoptosis. In addition to uveal melanomas, a number of other tumor cell lines of various cellular origins are sensitized to Fas-mediated cytotoxicity

by metalloprotease inhibitors that crack the membrane FasL into soluble FasL (sFasL), showing that sFasL, the autocrine secretion of FasL, shields tumor cells from Fas-mediated killing by cytotoxic lymphocytes (CD8+ CTLs). This defines a novel mechanism of tumor escape from immune surveillance, and the data of Nadal et al. strongly indicated that an increment of soluble FAS/sFASL ratio after treatment could be an excellent marker of chemosensitivity in colorectal cancer. On the other hand, a decreased ratio after treatment can be a predictor of chemoresistance despite an initial response[42, 43]. In addition, it was found that some tumor cells divided from U-87MG glioblastoma contain the stem cells marker CD133 and could tolerate FasL-induced apoptosis, suggesting that it would better to induce these tumor stem cells differentiation first in order to enhance the effect of immunotherapy [44].

6.Conclusion

The mechanisms of tumor immune escape are so diversity that it has decided the complexity of antitumor immunotherapy. Even though, immunotherapy is developed and could still be considered to as a best way, as the combined immune therapy ever mentioned above, and adopting effective antitumor strategies will have positive affections on clinical tumor immunotherapy.

Nevertheless, there are still many problems need to be deeply studied to utilize the immunotherapy more effectively, such as the utilization of immature DCs might induce immune tolerance, and over-stimulation might result in DCs immune no response and depletion. Although, along with the deeper and deeper researches on the mechanisms of tumor immune escape, more and more molecular mechanisms have been disclosed, and increasing mature immunotherapy strategies have been presented, the tumor immunotherapy must have a shine day in the future.

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