Tumor Immune Escape and Treatment

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Abstract. Tumor immune escape is one of the ten characteristics of tumor occurrence and development. Immunotherapy targeting immune escape has achieved remarkable success in recent years. Immunotherapy involves many factors and links, which are related to the changes of tumor cells themselves and tumor microenvironment, and the mechanism is complex. At present, it still faces great challenges in clinical practice. This article introduces the mechanism of tumor immune escape from several aspects, including the changes of tumor itself, the changes of tumor induced microenvironment, and the tumor microenvironment promoting tumor development. At the same time, in view of these mechanisms, the current treatment strategies were sorted out, including the predicament and progress of immune checkpoint inhibitors, CAR-T therapy and immune cell therapy, aiming to clarify the ideas for the next development of tumor immunotherapy.

Keywords: Tumor Escape; Tumor Microenvironment; Immunotherapy.

1. Introduction

Tumor immune escape is one of the ten essential characteristics of tumor occurrence and development. Its mechanism is very complex, involving genes, metabolism, inflammation, blood vessels and other links. Clarifying the mechanism of immune escape is helpful to find new targets. This article reviews the mechanism of tumor immune escape and the new progress of corresponding treatment strategies, aiming to clarify the ideas for the next development of tumor immunotherapy. At the same time, in recent years, people have devoted themselves to the study of the mechanism of tumor immune escape. In order to improve the immunogenicity of the tumor, stimulate the specific and non-specific immune response of the body, and promote the extinction of the tumor. The continuous discovery and in-depth study of oncogenes, the continuous expansion and deepening of the functions of various cytokines and immune stimulatory molecules have provided a strong theoretical basis for tumor immunotherapy. The above also reflects the research significance of this paper (HANAHAN & WEINBERG, 2011).

2. Mechanisms of Immune Escape in Tumors

Tumors can occur in the human body and continue to develop, because tumor cells in the long-term formation process, the formation of multiple immune escape mechanisms, escape from the immune system monitoring (BHATIA & KUMAR, 2014), the body's immune system appears obstacles, unable to recognize and kill tumor cells. Tumors can evade the immune system in the following ways:

(1) Weak immunogenicity and antigenic modulation of tumor antigens. (2) Decreased or defective expression of MHC molecules on the surface of tumor cells, or defective LMP and TAP for processing and presenting antigenic peptides. (3) Tumor cells convey inhibitory signals to NK cells by expressing non-classical HLA molecules (HLA-J and HLA-E) and down-regulate the function of NK cells to escape the attack of NK cells (GAO et al., 2014). (3) Tumor cells can autocrine or paracrine some immunosuppressive cytokines, such as IL-10 and TGF-β, to weaken the rejection effect of the immune system to the tumor or induce immunosuppressive cells to induce immunosuppression. (5) The expression of co-stimulatory molecules and adhesion molecules decreased. (6) Tumor cells can release soluble antigen molecules and combine with antibodies to form a complex, which binds to Fc receptors of lymphocytes, NK cells and macrophages through the Fc segment of antibodies, thus blocking the ADCC effect. (7) Tumor cells secrete soluble ligands of activated receptors, such as MICA, a ligand of NK cell-activated receptor NKG2D, which downregulates the
expression of activated receptors on the surface of immune cells, resulting in loss or decline of the function of immune effector cells. (8) High expression of FasL in tumor cells can mediate the apoptosis of tumor-specific T cells through the FasL–Fas pathway. On the other hand, low expression of Fas in tumor cells or defects in some FasL signaling molecules can resist FASL-mediated apoptosis. These mechanisms of immune escape do not exist in isolation. The same tumor may have multiple ways of immune escape. Different tumors and different stages of tumor differentiation may have different ways of immune escape (JAKOBSSON et al., 2012).

3. Management of Tumor Immune Escape

(1) Looking for tumor antigens. It is now recognized that tumor cells have tumor antigens, that is, tumor cells more or less express tumor antigens different from normal cells, but in general, the study of tumor antigens is still in the exploratory stage. The main reason is that the specificity of tumor antigen is not high and the immunogenicity is not strong. The same type of tumor in different individuals and the same tumor in different organs often do not express the same related antigens. The tumor expressed different antigens in different differentiation stages. A large number of tumor antigens lack effective processing and presentation.

In view of the above factors, on the one hand, people are trying to find new tumor-specific antigens, on the other hand, they are trying to enhance the immune rejection by enhancing the antigenicity of tumors. In the past decade, many human tumor antigens, such as MAGE, p53 and MUC-1, have been isolated and identified by using xenoseraums, CTL clones, monoclonal antibodies and molecular biological techniques. As to decipher the human genome sequence, bioinformatics and the progress of the new immune analysis technology, enabling people to by identifying gene expression in tumor gene expression, based on HLA immunogenicity base sequence prediction table, rebuild the antigen epitope of tumor cells, to enhance lymphocyte effect on tumor cell specificity of recognition and destruction, ELISPOT and Tetramer techniques were used to qualitatively and quantitatively analyze peptide-specific T cells at the single-cell level. Therefore, the combination of tumor genome and tumor immunotherapy will screen out a batch of new tumor antigens for the development of tumor vaccines, which will greatly promote the prevention and treatment of cancer.

(2) Enhance Tumor Antigenicity. In enhancing tumor antigenicity, people have adopted a variety of methods, including MHC, TAP and other genes. Introduce into tumor cells or induce the expression of TAP and MHC with IFN-γ; restore or promote the expression of MHC molecules and their presented antigen peptides on tumor cells, and enhance the sensitivity of CTL to kill tumors.

In addition, the reconstruction of costimulatory molecules can also be selected, and the genes of costimulatory molecules such as B7.1 and B7.2 can be introduced into tumor cells to mediate the adhesion between tumor cells and lymphocytes, enhance the antigen presentation function, and improve the Recognition of lymphocytes. However, in the tumor cells with weak immunogenicity, the introduction of costimulatory molecules alone cannot play a role, and the presence of appropriate antigen signals and other related factors is still required. Transfer cytokines to stimulate immune rejection, and transfer some cytokine genes, such as IL-2, TNF, etc. to tumor cells, so that tumor cells secrete cytokines in large quantities, activate local immune cells in tumors, and promote T and B Cell differentiation and proliferation, improve the body's anti-tumor ability. Reconstruction of antigen presentation function. The fusion of tumor cells with activated B cells and dendritic cells can correct the expression defects of MHC molecules and costimulatory molecules in tumor cells and improve the antigen presentation function. Block the resistance of tumor cells to Fas-mediated apoptosis. In tumors that do not express or low express Fas molecules or are resistant to FasL-mediated apoptosis, increasing Fas expression by transfection of Fas cDNA can induce tumor cell sensitivity to FasL-induced apoptosis; or block the tumor cell surface FasL, protects H cells from counterattack by tumor cell FasL. Since most tumor cells are of Th2 type, they can secrete Th2 cytokines and inhibit cellular immune response. Th1 cytokines or antibodies against Th2 cytokines can be used to transform tumor cells from Th2 type to Th1 type. It reduces the production of inhibitory cytokines and makes tumor cells more sensitive to the killing of T cells and NK cells.

(3) Enhance the body's anti-tumor effect. In order to improve the body's anti-tumor immune response, non-specific stimulants (such as BCG, Corynebacterium pumilus, etc.) or various cytokines are used to stimulate the body's immune system and enhance the anti-tumor immune response. More importantly, the use of tumor vaccines to stimulate the body's specific immune response. Adoptive cellular immunotherapy is the infusion of specific and non-specific tumor killer cells and other effector cells, such as LAK cells, NK cells, etc., into patients to expand the role of anti-cancer effector cells and exert anti-tumor effects in vivo. NK cells are important anti-tumor effector cells in the body. They not only have a lytic and killing effect on tumor cells, but also act on CD4+ T cells and CD8+ CTL to strengthen acquired immunity, so they have important immune regulation functions. In recent years, it has been found that there are killing inhibitory receptors (KIR) on the surface of NK cells that recognize MHC molecules on the surface of tumor cells. KIR recognizes MHC molecules and transmits negative signals to NK cells. When the expression of MHC molecules on the surface of tumor cells is defective or mutated, the inhibitory signal recognized by NK disappears, thereby exerting a killing effect on tumor cells. It can be seen that tumor cells with deletion or mutation of MHC class I antigens can escape the immune surveillance of cells, but become sensitive to NK and killed by NK cells. The different results of NK and CTL recognition of MHC class I molecules. The functions of the two complement each other and jointly complete the immune surveillance task of the body.
4. Tumor Immunotherapy

The occurrence and development of tumors involve many factors, and tumor formation is the result of the combined action of multiple genes and multiple factors. The study of the mechanism of tumor immune escape has deepened people's understanding of the arduousness of tumor immunotherapy. Tumor heterogeneity determines the complexity of tumor treatment. Taking tumor MHC deficiency as an example, the expression of MHC class I molecules on the surface of most tumor cells is decreased or absent. The loss of HLA molecules in human tumors includes complete loss of HLA molecules, haplotype loss, loss of a certain locus, and loss of HLA alleles. A variety of mechanisms are involved in the change of HLA phenotype, such as TAP synthesis disorder, HLA class I gene insertion, deletion or point mutation. Different tumor types, locations and development stages have different HLA expression, showing the complexity of HLA expression. Even the same tumor of the same individual is heterogeneous, and the HLA phenotypes of different cell clones are not consistent and may mutate during development. Some scholars believe that the essence of tumor cells is micro-evolution, that is, tumor cells have acquired genetic adaptability in the long-term evolution process, and after multi-step selection, they form tumor cells with high adaptability. Therefore, the mechanism of tumor immune escape is not a single one, but a combination of multiple escape mechanisms, and in different tumors or different differentiation stages of the same tumor, the mechanisms of immune escape are also different. Correspondingly, the prevention and treatment of tumors also need to involve multiple disciplines and multiple methods, which cannot be solved by a single discipline or a single technology. Surgery, chemotherapy, and radiotherapy are indispensable adjuvant treatments. It is generally believed that when the total volume of the tumor in the body does not exceed 1 cubic centimeter, tumor immunotherapy may play an important role, and the activation of immune cells or immune molecules first needs to overcome the immune escape phenomenon of the tumor, otherwise the immune function of the body cannot be exerting an effect. When the total volume is greater than 1 cubic centimeter, surgery, radiotherapy, and chemotherapy must be used to remove the tumor, and the residual tumor cells should be hit multiple times with different attributes, so that the residual tumor cells have not evolved to adapt to a certain method. Extinct by successive blows of different nature, among which immunotherapy plays a very important role in preventing tumor recurrence and metastasis. According to the characteristics of different tumors, the combined application of multiple tumor immunotherapy methods will achieve better results.

5. Conclusion

To sum up, there is an extremely complex dialectical relationship between the immune escape mechanism of tumors and the body's immune response to tumors. And to determine the research and treatment plans for different tumor cells, different disease stages, and different individuals, and enhance the body's immune and anti-tumor capabilities, it is possible to make breakthroughs in the treatment of tumors from the perspective of immunological rejection.

References
