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Molecular Mechanisms of Immune Evasion in Cancer

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Introduction

The immune system plays a pivotal role in protecting the body from cancer by recognizing and eliminating abnormal or transformed cells. However, many cancers have developed sophisticated mechanisms to evade immune detection and destruction, allowing tumors to grow and metastasize unchecked. This ability of tumors to escape immune surveillance is known as immune evasion. Understanding the molecular mechanisms underlying immune evasion in cancer is crucial for developing more effective immunotherapies, such as immune checkpoint inhibitors and cancer vaccines. In this article, we will explore the various ways in which cancer cells manipulate the immune system to promote tumor growth and survival, and how these insights are guiding therapeutic advances [1].

Description

Immune checkpoint molecules and t cell inhibition

One of the most well-characterized mechanisms of immune evasion in cancer involves the upregulation of immune checkpoint molecules. These molecules are normally expressed on immune cells and serve to dampen immune responses in order to prevent excessive inflammation or autoimmunity. However, tumors often exploit these checkpoints to inhibit T cell activity and suppress anti-tumor immunity [2]. The key immune checkpoint molecules involved in cancer immune evasion include PD-1 (Programmed Cell Death Protein 1), CTLA-4 (Cytotoxic T-Lymphocyte Antigen 4), and LAG-3 (Lymphocyte Activation Gene 3).

PD-1/PD-L1 axis: PD-1 is a receptor expressed on T cells that, when engaged by its ligand PD-L1 (often overexpressed on tumor cells), sends an inhibitory signal that reduces T cell activation and function. This immune checkpoint is a major mechanism by which tumors escape immune surveillance, as PD-L1 expression on tumor cells or the tumor microenvironment helps tumors evade destruction by cytotoxic T lymphocytes (CTLs) [3].

CTLA-4: CTLA-4 is another immune checkpoint receptor expressed on activated T cells. It competes with CD28, a co-stimulatory receptor, for binding to ligands on antigen-presenting cells (APCs). When CTLA-4 binds to these ligands, it inhibits T cell activation and promotes immune tolerance. Many tumors exploit this pathway to reduce the effectiveness of the immune system's anti-tumor response. The discovery of immune checkpoint inhibitors, such as pembrolizumab (anti-PD-1) and ipilimumab (anti-CTLA-4), has revolutionized cancer immunotherapy by blocking these inhibitory signals and enhancing T cell-mediated anti-tumor immunity [4].

Regulatory T Cells (Tregs) and myeloid-derived suppressor cells

Regulatory T cells (Tregs) are crucial in maintaining immune tolerance and preventing autoimmunity. However, in the context of cancer, Tregs can be co-opted by tumors to suppress the immune response against cancer cells. Tumor cells can attract Tregs into the tumor microenvironment through the secretion of chemokines such as CCL22, and the presence of Tregs can inhibit the activation of cytotoxic T cells and NK cells, allowing the tumor to grow unchecked. Similarly, myeloid-derived suppressor cells (MDSCs) are a heterogeneous population of immature myeloid cells that accumulate in cancerous tissues. MDSCs are potent inhibitors of immune responses, primarily by producing immunosuppressive cytokines, such as IL-10 and TGF-β, and by directly inhibiting T cell activation. They also interfere with dendritic cell function, further reducing the ability of the immune system to mount an effective anti-tumor response [5].

Loss of tumor antigen expression and antigen presentation

Tumor cells can also evade immune detection by downregulating the expression of tumor-associated antigens or by impairing antigen presentation. Tumor-associated antigens (TAAs) are proteins that are either uniquely expressed or overexpressed in tumor cells and are recognized by the immune system as potential targets. However, tumor cells can reduce the expression of these antigens or undergo antigen loss variants, making it more difficult for immune cells to recognize and target them. Another important mechanism of immune evasion involves the downregulation of major histocompatibility complex (MHC) molecules, which are essential for presenting tumor antigens to T cells [6]. MHC class I molecules present intracellular antigens to cytotoxic T cells, while MHC class II molecules present antigens to helper T cells. Tumor cells often downregulate MHC expression, thereby reducing their visibility to the immune system.

Metabolic reprogramming of tumor cells: Tumors often undergo metabolic reprogramming to support rapid growth and survival. This metabolic shift can also influence the immune system. For instance, tumor cells frequently exhibit altered glucose metabolism (the Warburg effect) and release metabolites such as lactate and adenosine into the tumor microenvironment. These metabolites can impair immune cell function by creating an acidic, low-oxygen environment that inhibits T cell activation and enhances the immunosuppressive activity of Tregs and MDSCs [7,8].

Conclusion

Immune evasion is a hallmark of cancer progression and involves a multifaceted array of molecular mechanisms that enable tumors to

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escape immune surveillance. From immune checkpoint molecules that inhibit T cell function to the creation of an immunosuppressive microenvironment by tumor-derived cytokines and regulatory cells, cancer cells have evolved numerous strategies to protect themselves from immune attack. Understanding these mechanisms is crucial for developing more effective immunotherapies, such as immune checkpoint inhibitors, adoptive T cell therapies, and cancer vaccines, which aim to reinvigorate the immune system's ability to recognize and destroy tumor cells.

Acknowledgement

Conflict of Interest

None

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