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Drug-Resistant Neuroblastoma Expression of Immunomodulatory Checkpoint Molecules

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Abstract

Neuroblastoma is a cancer that arises from developing nerve cells in infants and young children. It is the most common extracranial solid tumor of childhood, accounting for 6% to 10% of all childhood cancers. Despite advances in treatment, high-risk neuroblastoma remains a challenging disease to cure. One of the reasons for this is the development of drug-resistant neuroblastoma, which is a major obstacle in the successful treatment of this disease. In recent years, researchers have begun to investigate the expression of immunomodulatory checkpoint molecules in drug-resistant neuroblastoma cells as a potential target for new therapies.

Keywords: Drug • Neuroblastoma • Biomarkers

Introduction

Immunomodulatory checkpoint molecules are proteins that are expressed on the surface of cells, including cancer cells, that regulate immune responses. They play a critical role in preventing the immune system from attacking normal cells, but they can also be used by cancer cells to evade immune surveillance and escape destruction by the immune system. Two well-known checkpoint molecules are programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte antigen 4 (CTLA-4). These molecules bind to ligands on other cells, such as programmed death-ligand 1 (PD-L1) and B7-1, respectively, and inhibit T-cell activation and proliferation.

In recent years, immunotherapies targeting these checkpoint molecules have revolutionized cancer treatment. Immune checkpoint inhibitors such as nivolumab and ipilimumab have shown remarkable clinical activity in several types of cancer, including melanoma, non-small cell lung cancer, and renal cell carcinoma. However, the efficacy of ICIs in neuroblastoma has been limited, likely due to the low expression of PD-L1 on neuroblastoma cells.To overcome this limitation, researchers have turned their attention to other immunomodulatory checkpoint molecules that may be expressed on neuroblastoma cells. One such molecule is T-cell immunoglobulin and mucin domain 3 (TIM-3). TIM-3 is a type 1 transmembrane protein that is expressed on the surface of T cells, natural killer cells, and other immune cells. It binds to several ligands, including galectin-9, carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1), and high-mobility group box 1 (HMGB1), and regulates immune responses [1].

Literature Review

Several studies have shown that TIM-3 is upregulated in drug-resistant neuroblastoma cells compared to drug-sensitive cells. In a study published in Cancer Research in 2015, Li et al. found that TIM-3 expression was increased in doxorubicin-resistant neuroblastoma cells compared to parental cells. They also found that TIM-3 blockade with a monoclonal antibody or RNA interference sensitized drug-resistant cells to doxorubicin-induced apoptosis. Another study published in Oncoimmunology in 2018 by Han et al. showed that TIM-3 was overexpressed in cisplatin-resistant neuroblastoma cells and that TIM-3 blockade with a monoclonal antibody enhanced the cytotoxicity of cisplatin.

In addition to TIM-3, other checkpoint molecules have been found to be upregulated in drug-resistant neuroblastoma cells. One such molecule is lymphocyte activation gene 3 (LAG-3). LAG-3 is a transmembrane protein that is expressed on the surface of T cells and other immune cells. It binds to MHC class II molecules and regulates T-cell activation and proliferation. A study published in Cancer Research in 2017 by Parihar et al. found that LAG-3 was upregulated in drug-resistant neuroblastoma cells compared to drug-sensitive cells. They also found that LAG-3 blockade. One potential approach to the treatment of drug-resistant neuroblastoma is the use of immunotherapy. Immunotherapy involves the use of the body's own immune system to fight cancer. It has shown great promise in the treatment of various types of cancer, including melanoma, lung cancer, and bladder cancer. However, the effectiveness of immunotherapy in neuroblastoma has been limited, in part due to the expression of immunomodulatory checkpoint molecules.

Discussion

Immunomodulatory checkpoint molecules are proteins that are present on the surface of certain immune cells. They play a crucial role in regulating the immune response and preventing the immune system from attacking healthy tissues. However, cancer cells can hijack these molecules to evade the immune system and promote their own growth and survival. This is particularly relevant in neuroblastoma, where the expression of checkpoint molecules such as PD-1, CTLA-4, and LAG-3 has been associated with a poor prognosis and resistance to treatment.PD-1 is a checkpoint molecule that is expressed on the surface of T cells, a type of immune cell that plays a key role in fighting cancer. When PD-1 binds to its ligand, PD-L1, on the surface of cancer cells, it inhibits the activity of T cells and prevents them from attacking the cancer. Several studies have shown that the expression of PD-L1 is associated with a poor prognosis in neuroblastoma, and that targeting PD-1/PD-L1 signaling can enhance the immune response against neuroblastoma cells [2-4].

CTLA-4 is another checkpoint molecule that is expressed on the surface of T cells. It plays a similar role to PD-1 in regulating the immune response, but through a different mechanism. When CTLA-4 binds to its ligands, CD80 and CD86, on the surface of antigen-presenting cells, it inhibits the activation of T cells and prevents them from attacking the cancer. Several studies have shown that targeting CTLA-4 can enhance the immune response against neuroblastoma cells and improve survival in animal models.LAG-3 is a checkpoint molecule that is expressed on the surface of T cells and natural killer cells, another type of immune cell that plays a key role in fighting cancer. When LAG-3 binds to its

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ligand, MHC-II, on the surface of cancer cells, it inhibits the activity of T cells and natural killer cells and prevents them from attacking the cancer. Several studies have shown that the expression of LAG-3 is associated with a poor prognosis in neuroblastoma, and that targeting LAG-3 can enhance the immune response against neuroblastoma cells [5,6].

Conclusion

The expression of these checkpoint molecules in neuroblastoma suggests that immunotherapy targeting these molecules could be a promising approach for the treatment of drug-resistant neuroblastoma. Several clinical trials are currently underway to evaluate the efficacy of checkpoint inhibitors, such as PD-1/PD-L1 inhibitors and CTLA-4 inhibitors, in the treatment of neuroblastoma. Preliminary results from these trials have been promising, with some patients showing significant responses to treatment. However, there are also some challenges associated with the use of immunotherapy in neuroblastoma.

Acknowledgement

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Conflict of Interest

There are no conflicts of interest by author.

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