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# 1-MHC as a target for cancer treatments

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**Abstract.** Class-1 Major Histocompatibility Complex (MHC) molecules plays an important role in the immune system by exposing antigens to T cells for identification and destruction. Cancer cells often evade the immune system by downregulating MHC expression, avoiding detection from immune cells. Therefore, Class-1 MHC molecules are potential targets for cancer treatments. Recent studies have shown that increasing MHC expression in cancer cells can enhance T cell recognition and enhance the efficacy of immunotherapies, such as checkpoint inhibitors and adoptive cell transfer therapies. In addition, some therapeutic approaches are aimed at directly targeting Class-1 MHC molecules. This paper summarizes the mechanism of MHC expression, the current status of cancer treatments, relevant research status of class-1 MHC as a target in cancer therapy, and how this technique can be improved. These findings highlight the potential of Class-1 MHC as a promising target for cancer treatment, and further research is needed to fully exploit this target for the benefit of cancer patients.

**Keywords:** Class-1 MHC, immunotherapy, cancer.

## 1. Introduction

The current treatments for cancer contain mainly three methods, including chemotherapy, radiotherapy, and surgical treatment. In this part of the articles, article analyzes the present situation of chemotherapy, radiotherapy and surgical treatment as well as a new method -Tumor targeted therapy. The common chemotherapy can be separated into two ways: Oral ingestion and Intravenous injection. After taking anti-cancer drugs, they circulate in the blood to the whole body to target cancer cells and effectively delay the development of tumor and improve the overall condition of patients. Compared to surgical treatment and radiotherapy, the advantages of chemotherapy is obvious that the drugs will spread throughout most organs and tissues of the body with blood circulation. Therefore, chemotherapy is the main treatment for some cancers that have the tendency of systemic dissemination and metastasized terminal cancer [1]. The side effects of chemotherapy is the destruction of normal cells including blood-forming cells in the bone marrow, hair follicles, cells in the mouth, digestive tract, and reproductive system [2]. Tumor radiotherapy is a local treatment method that uses radiation (Radioisotope α, β, γ X-rays and various x-rays) to destruct DNA of tumors to cure patience. Radiotherapy has two purposes: one is to eliminate cancer cells in certain areas, and the other is to

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alleviate the pain caused by metastasis. Although the tumor may have spread from the primary site, it also can be treated with radiotherapy separately as long as the cancer is limited to local areas [1]. The side effects of Radiotherapy can be long-tern or short-term, and ordinarily, it contains tiredness, low blood cell level and even limited sex life [3].

Surgical treatment is a physical elimination of cancer cell which is still the most reliable method to treat cancer as it may genuinely eradicate tumor especially early and benign cancer. Therefore, the advantage of surgery is to increase the chance of curing cancer, but in reality, there are some cases of recurrence. Taking gastric cancer in case, the data shows that 70% of patients can be cured, but the remaining 30% will recur as cancer cells invisible to the naked eye cannot be removed during surgery and remain in the body [1]. Nowadays, thanks to the implication of laparoscopic operation, the operation is carried out with minimal pressure on body [1]. Targeted therapy is a method that targets proteins that dominates the tumor development [4]. With the analysis of these proteins, researchers can design drugs as specific targets complementary to the receptors on cancer cells. This therapy can not only help immune system target tumor cell and transmit cell-killing substances, but also deliver interrupting signals that prevent growing to the cancer cell as well [4]. Although this therapy has outstanding efficacy, the number tumor targeted therapy drugs are few, expensive and difficult to mass produce.

## 2. The class-1 MHC

### *2.1. What is MHC-class I*

Major histocompatibility complex (MHC) is a group of closely linked genes that are closely related to the immune response and determine the compatibility of transplanted tissues. It is ubiquitous in mammals. The presence of multiple alleles in the same locus of MHC is highly polymorphic. Human MHC is sometimes referred to as the HLA gene complex (human leukocyte antigen), and its encoded products are called HLA molecules or HLA antigens. In the early 20th century, it was found that rejection often occurred after allogeneic animal tissue and organ transplantation. It has been proved that the essence of graft rejection is the immune response of graft recipients to antigens expressed by donor tissue cell[5]. The antigens that determine the occurrence of graft rejection are called major histocompatibility antigens. Nevertheless, MHC encodes major histocompatibility antigens. The major roles of MHC antigens, which are widely dispersed on the surface of many cells, are to take part in antigen presentation, prevent cell-to-cell recognition, and trigger immune responses. MHC-class I and class II molecules mostly have a role in antigen presentation.

MHC class I molecules consist of an alpha chain and a β2 microglobulin (β2 m). The alpha chains are encoded by MHC-class I genes and are transmembrane proteins that are anchored to the cell membrane. Its molecular weight is 44kd and its structure is polymorphic. Its carboxyl terminus crosses the cell membrane and extends into the cytoplasm. The amino terminus is free from the cell membrane. MHC class I molecules are divided into extracellular, transmembrane, and intracellular segments. The 1, 2, and 3 domains are present in the extracellular section. Among them, α1 and α2 domains are the basis for determining the polymorphism of MHC-I molecules. The antigen-binding groove, which is closed at both ends and may hold peptides of about eight to eleven amino acid residues, is formed by the combination of the 1 and 2 domains. A non-MHC gene on chromosome 15 codes for the non-transmembrane protein 2m [6]. This chain is polymorphic and interacts noncovalently with the α3 domain of the α chain and is involved in maintaining the stability of the native configuration of MHC class I molecules.

During human immune response,MHC-I molecules has the important responsibility of presenting antigens to CD+8T cells. In the process of antigen presentation, T cells not only recognize the antigen peptide presented by APC, but also recognize the MHC molecules bound to the antigen peptide, which is the restricted recognition of T cells. Thus, MHC-I molecules also restrict CD8+T cell[7]. MHC-I molecules are involved in regulating NK cell activity. NK cells express inhibitory receptors on the NK cells' cytomembranes, which can bind to their own MHC class I molecules to initiate inhibitory

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signals and inhibit NK cell activity. So normal cells are protected from killing. If the expression of MHC-I molecules on the cytomembranes is reduced or absent, such as cancer cells and some virus-infected cells, the inhibitory signal of NK cells disappears, leading to the activation and killing of NK cell[8].

### *2.2. Current status of class-1 MHC in cancer therapy*

On the clinical front, tumor immunology's MHC-mediated antigen exhibition and T-cell receptor distinction pathways may open the door to novel therapeutic strategies. Less recognition and cytotoxicity of CD8+ T cells are caused by the downregulation of the MHC-I, a key mechanism by which solid tumors can resist anticancer response[9]. The T cell receptor (TCR) targets of CD8+ T cells can only be bound by MHC-I, represented on all nucleated cells. In order to elicit CD8+ T cell responses, endogenous antigens are presented by MHC-I. This crucial program alerts the immune system to intracellular alterations, such as those brought on by viral infection or malignanc[10]. The heterodimeric MHC-I comprises heavy chains and invariant light chains known as 2-microglobulin (2M), encoded by the human leukocyte antigen(HLA-A, HLA-B, and HLA-C). The antigen-processing machinery loads the MHC-I peptide-binding groove with peptides to stabilize heterodimers (APM). The lower the MHC-I expression level, the more vulnerable the cell is to NK cell-mediated cytotoxicity, even though it can be cut to enable evasion of T cell-mediated antitumor immunity. MHC-I works as an inhibitory ligand for NK cells, blocking NK cell activation when it binds to corresponding receptors. Hence, MHC-I-initiated inhibitory signals are absent when MHC-I is downregulated, boosting NK cell activation and cytotoxicit[11]. MHC I The intrinsic reversibility of these dysregulations supplies a chance to restore the MHC class I molecule's expression. As an activator of MHC class I molecules, NLCR5 can participate in the pathogenesis of colon cancer and affect its prognosis, mediate the upregulation of the expression of MHC class I, and also help improve the effect of immunotherapy and resist tumor immune escape. Due to the limitations of MHC molecules, most of the immunotherapy methods involving T cell recognition are limited to the patients themselves, which is one of the reasons for the high cost of immunotherapy, which makes it challenging to popularize treatment programs that require huge costs in tumor patients; secondly, tumor cells are prone to Immune escape occurs, and then metastasizes and recurs to other parts of the patient's body; moreover, a complete evaluation system for the effect of tumor immunotherapy has not been established clinically. However, with the deepening of people's understanding of the occurrence and development of tumors, the diagnosis and treatment of tumor immunology will flourish, and the research on MHC molecules and immunotherapy will become a new focus and direction [12].

### *2.3. Problems and technology*

MHC is an abbreviation for major histocompatibility complex for all vertebrates. It was discovered during the early 20th century from the rejection of tumors between genetically different mice [13]. Since then, further research shows that there are two different groups of MHC, one is MHC - class 1 and the other is MHC - class 2. Between the two classes, the primary distinction is that all vertebrate nucleated cells have MHC-class 1 molecules on their surfaces, but MHC-class 2 molecules are mostly found on antigen-presenting cells such as B cells and macrophages [14]. Due to the properties of MHC - class 1 molecules to bind with peptides created from a cell’s genes and carrying the peptides and display the endogenous antigens on the cell’s surface; the CD8 T Cells in the body examines the antigens on the surface of the cell and identify whether or not the cells is producing unusual proteins, which is what cancer cells do. No matter what cell it is, the MHC - class 1 molecule presents the antigens of every protein of the cells, which is then scanned by the natural killer T cells that contain CD8+ receptors that bind to the MHC - class 1 molecule [15]. If the killer T cells does identify something unusual regarding the antigens of the cell, the T cell will immediately destroy the cell. This identification process between MHC - class 1 and CD8+ T cells is an immune mechanism in the body that destroys cells that present excessive amounts or foreign antigens, which are usually cells that are cancerous or malignant [14]. Furthermore, for most animals, the MHC - class 1 is made up of three

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genes. Specifically, for humans, the MHC - Class 1 is constructed from HLA-A, HLA-B and HLA-C. All three of these genes that encode MHC - class 1 are polymorphic, meaning it has many different multiple binding docks that recognize its own peptides [16]. The diversity of the MHC – class 1 genes helps the immune system to identify a vast array of different antigens and help defend against invading viruses or pathogens.

From the relationship between CD8+ T cells and MHC – class 1 molecule, and the variety of MHC – class 1 genes, the researchers are able to develop many ways to treat cancer such as immune checkpoint inhibitors, tumor vaccines and adoptive cell therapies. However, why is a person still able to develop cancer when there is such a function of the immune system? It is because the tumor can escape the detection of CD8+ T cells by decreasing the MHC - class 1 molecules. Research showed that a tumor in the Tasmanian Devil, a small mammal, is able to develop T cell immunity by reducing MHC - class 1 expression [17]. Another research indicates that melanoma cells with MHC - class 1 down regulation are more capable of developing and spreading tumors than the cells that lose fewer MHC - class 1 allele during down regulation [18]. In addition, a somatic mutation that occurs with the MHC - class 1 gene would lose the ability to bind with CD8 T cells or antigen recognition [19]. If the problem regarding the reduction of MHC is not solved, then cancer immunotherapy would work because the down regulation is going to proliferate more tumor cells around the patient's body. Thankfully, researchers are able to find strategies to deal with loss of MHC - class 1. One of the strategies is to enhance the IFNγ antigen that is present in the MHC - Class 1 pathway. Which will increase immunogenicity towards tumor cells and enhance the detection of CD8+ T cells [20]. Another way is the Anti-CTLA-4 therapies, where the CTLA-4 amplifies the activation level of T cells, which reduces immune response to weak antigens. This therapy proved to be successful as patients with melanoma that used this therapy are able to have drastic improvement and many countries have already approved its clinical usage [21].

## 3. Conclusion

This study assesses the suitability of MHC-I as a target for cancer therapy and presents a cross-section evaluation of the available cancer treatments. Chemotherapy and radiotherapy, as traditional cancer treatment methods, cause great damage to human normal tissues. Although surgical treatment is less invasive, there is still a risk of recurrence. The specificity and side effects of targeted therapy are higher than those of these three conventional treatments. MHC-I molecules are present in all mammalian cells and are directly associated to immunological responses. Antigen presentation and the generation of immune responses are two of their primary roles. MHC-I molecules have the ability to be targeted because MHC-I molecules are critical for antigen presentation by CD8+T cells, and tumor cells can achieve immune escape by reducing MHC-I molecules expression. At the same time, low MHC-I expression can sensitize cells to NK cell-mediated immune processes and enhance NK cell activity and cytotoxicity. There are currently two strategies to deal with MHC-I downregulation, which are enhanced IFNγ antigen and Anti-CTLA-4 therapy. Enhancing IFNγ antigen in the MHC-1 pathway can increase the immunogenicity of tumor cells, thereby enhancing the ability of CD8+T cells to recognize IFNγ antigen. The anti-CTLA-4 medication increases T cell function, T cell activity, and anti-tumor immune responses. Among them, Anti-CTLA-4 therapy has achieved some success in clinical practice. At present, many of the therapies targeting MHC-I are aimed at improving the activity of T cells, and there is a lack of studies that can improve MHC-I downregulation, which needs to be solved by further research. There is also a lack of drug development for the mechanism by which low MHC-I expression can enhance NK cell activity. Nevertheless, a methodical strategy for assessing the effectiveness of tumor immunotherapy in clinical settings is currently lacking, which makes it difficult to quantify the effect of targeted therapy, and also has a certain impact on the discovery of potential problems in therapy. However, with the development of various gene editing tools, such as CRISPR, and the progressive improvement in public knowledge of tumor-targeted treatment, the diagnosis and treatment of tumor immunology will flourish, and the research on MHC molecules and immunotherapy will become a new focus and direction.

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