Synergistic Mechanism of Functional Foods Rich in Active Peptides in Tumor Immunotherapy

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Abstract. Given that traditional tumor therapy is associated with recurrence risk and immunotherapy is limited by the tumor immune microenvironment, alternative adjuvant approaches are urgently needed. In this context, active peptide-functional foods have emerged as promising auxiliary resources, yet their synergistic anti-tumor mechanisms are still not well understood, necessitating further research. In this paper, the dual functions of active peptides in direct tumor suppression and bidirectional regulation of immunity were analyzed. The synergistic principle of inducing immunogenic cell death and activating systemic anti-tumor immunity was elucidated by Gramicidin S and its light-controlled derivatives. Four types of synergistic methods, including molecular modification, light-controlled administration, combination therapy, and nanocarriers, were summarized. It was pointed out that these peptides had problems such as lack of preparation standards and only stopping in vitro experiments. This study clarified the mechanism of active peptide combined with immunotherapy, and provided theoretical support for the development of anti-tumor active peptide food. The existing in vivo pharmacological data are insufficient, and the Immunogenic cell death (ICD) regulatory pathway can be further analyzed in the future, so as to improve the in vivo efficacy and standardized production research and promote its clinical transformation.

Keywords: Tumor immunotherapy; active peptides; synergistic mechanism.

1. Introduction

Malignant tumor is a major disease that endangers human health. Surgery, chemotherapy, and radiotherapy are routine clinical treatments. However, there are shortcomings such as strong trauma, easy drug resistance, difficulty in removing residual lesions, and high recurrence and metastasis rates. The overall treatment prognosis is limited. As a new generation of anti-tumor treatment paradigm, tumor immunotherapy mainly includes immune checkpoint blockade, CAR-T cell therapy, therapeutic tumor vaccine and other core technologies [1-3]. It has been widely used in clinical intervention of tumors, with significant efficacy in hematological tumors, and has gradually achieved breakthroughs in the treatment of solid tumors [4]. However, there are still obvious limitations in this therapy, such as tumor immune escape, tumor microenvironment immunosuppression, insufficient infiltration of immune cells in solid tumors, and treatment-related toxic and side effects, which seriously restrict clinical efficacy and application scope. It is urgent to explore safe and effective adjuvant synergistic methods to optimize the tumor immunotherapy regimen.

Functional food materials rich in active peptides have a wide range of sources, high safety, good absorbability, and dual biological activities (anti-tumor and immune regulation), making them a potential resource for tumor-assisted intervention. Related studies have shown that on the one hand, active peptides can directly inhibit tumor cell proliferation, induce tumor cell apoptosis, and block tumor invasion and metastasis; on the other hand, it can effectively regulate the immune function of the body, reshape the microenvironment of benign tumors, enhance the ability of immune surveillance, synergistically strengthen the effect of tumor immunotherapy, and make up for the defects of existing treatment [5]. At present, active peptides have been gradually applied in the field of tumor prevention and assisted rehabilitation, but there are still problems such as unclear mechanism of action, insufficient targeting, and immature industrial application. Based on this, this study focused on the synergistic mechanism of functional food rich in active peptides in tumor immunotherapy, and carried

out systematic exploration, aiming to clarify the internal mechanism of active peptides enhancing anti-tumor immunity, and provide scientific theoretical basis and practical reference for the development, application and clinical transformation of functional food-assisted tumor therapy.

2. Core Functions of Active Peptides

2.1. Anti-tumor Effect

The active peptide initially adheres to the tumor cell membrane via charge adsorption, thereby disrupting the integrity of its lipid structure, inducing the leakage of intracellular contents, and ultimately leading to tumor cell necrosis. Active peptides that successfully enter the cell will target mitochondria, damage mitochondrial structure and function, block cell energy supply, and ultimately induce programmed apoptosis of tumor cells [6]. At the same time, active peptides can also regulate the cell cycle of tumor cells, block the process of cell division, and inhibit the infinite proliferation of tumor cells from the root [5]. In the middle and late stages of tumor progression, active peptides can inhibit tumor angiogenesis, cut off the nutritional and material transport channels of tumor tissues, and gradually atrophy the tumor lesions due to insufficient blood supply. It can also down-regulate the activity of proteases related to tumor invasion and metastasis, hinder the infiltration of tumor cells into surrounding tissues and distant metastasis, and limit the malignant progression of tumors in an all-round way [7].

2.2. Immunomodulatory Effect

Active peptide has a comprehensive regulatory ability to the body's immune system, which can act on both innate immunity and adaptive immunity, balance the intensity of immune response, and improve the overall immune status. At the innate immune level, active peptides can activate core immune cells such as macrophages, natural killer cells (NK cells), T lymphocytes and B lymphocytes, enhance the proliferation, phagocytosis and tumor killing ability of immune cells, and strengthen the body 's removal efficiency of abnormal cells and pathogens. At the level of humoral immunity, active peptides can stimulate the body to secrete immunoglobulins such as IgA, IgG, and IgM. Among them, secretory IgA can strengthen the intestinal mucosal immune barrier and reduce the risk of secondary infection in cancer patients [8].

Cytokines are key signaling molecules that regulate immune responses, and active peptides can achieve two-way balance regulation of cytokines. When the body needs to strengthen immune defense, active peptides can up-regulate the expression of pro-inflammatory factors such as IL-12 (Interleukin-12) and IFN-γ (Interferon-γ) and amplify the immune effects of anti-infection and anti-tumor. When the body is stimulated by pathogens and produces an uncontrolled and excessive inflammatory response, peptides can effectively down-regulate key pro-inflammatory factors such as TNF-α (Tumor Necrosis Factor-α), IL-6, and IL-1β secreted by macrophages and dental pulp fibroblasts. Blocking the continuous cascade amplification of inflammatory signals, alleviating the local inflammatory disorder, preventing excessive activation of immune cells from infiltrating and releasing toxic mediators, thereby avoiding irreversible inflammatory damage to the normal soft and hard tissues of the dental pulp and periapical [9]. This two-way regulation feature allows active peptides to effectively improve the coexistence of immunosuppression and chronic inflammation in cancer patients.

3. Synergistic Mechanism of Active Peptide and ICD-induced Immunotherapy

Active peptides can form a synergistic effect with tumor immunotherapy by directly killing tumor cells and triggering immunogenic cell death (ICD), so as to achieve efficient overcoming of tumors from the dual levels of cytotoxic killing and immune activation. Gramicidin S (GS) and its light-controlled derivatives LMB002 and LMB033 used in the study of Yamei Liu et al. are the core active peptide molecules that mediate this synergy [10]. Brevibacterium peptide S is a natural cyclic cationic

antimicrobial peptide, which can destroy the lipid bilayer of tumor cell membrane in a receptor-independent manner and cause cell lysis and death. Its light-controlled analogues LMB002 and LMB033 are modified by diarylethene fragments to have two photoisomers of visible light-activated open type and ultraviolet light-activated closed type. Among them, the open isomer retains the strong cytotoxicity consistent with the parent GS, and the closed isomer toxicity is significantly reduced, which not only guarantees the local precise killing of the tumor, but also reduces the non-specific damage to normal cells. Both two-dimensional monolayer cells and three-dimensional tumor sphere models showed selective killing effect on tumor cells.

By precisely triggering the ICD process, immune-silenced tumor cells are transformed into immune-activated signal sources to reshape the tumor immune microenvironment and initiate a systemic anti-tumor immune response [10]. In the process of action, the active peptide can induce tumor cells to rapidly release adenosine triphosphate (ATP) at sub-IC50 concentration, and extracellular ATP acts as a key chemotactic signal to recruit and activate antigen-presenting cells such as dendritic cells. At the same time, it triggers endoplasmic reticulum stress, promotes the translocation of calreticulin (CALR) from the endoplasmic reticulum to the surface of the cell membrane, transmits ' phagocytosis signals ' to antigen-presenting cells, and improves the efficiency of tumor antigen uptake and presentation. It can also promote the release of high mobility group protein B1 (HMGB1) from the nucleus to the outside of the cell, promote the maturation of antigen-presenting cells by activating RAGE, TLR and other pathways, and break the immunosuppressive state of tumor. Under the synergistic effect of the direct killing of active peptides and ICD-mediated immune activation, tumor cells are rapidly eliminated, while tumor-associated antigens and new antigens are effectively presented, thereby inducing the proliferation and activation of cytotoxic T lymphocytes and helper T cells, forming a specific anti-tumor immune response, and establishing long-term immune memory, inhibiting tumor residue, invasion and metastasis. Among them, LMB033 shows better application potential in synergistic anti-tumor due to its higher light-controlled switching efficiency and more significant ICD induction effect.

4. Strategies to Enhance the Synergistic Effect of Active Peptides

Active peptides can form an efficient synergy with immunotherapy by directly killing tumor cells and triggering immunogenic cell death (ICD) to accurately overcome tumors. Yamei Liu et al. used Gramicidin S (GS) and its light-controlled derivatives LMB002 and LMB033 as core active peptides [10].GS is a natural cyclic cationic antimicrobial peptide that can destroy tumor cell membranes in a receptor-independent manner and cause lysis and death. LMB002 and LMB033 were modified by diarylethene, and there were open and closed photoisomers. The toxicity and ICD induction ability of open isomers were close to GS, and the activity of closed isomers was significantly reduced. Both targeted killing and low systemic toxicity advantages showed good tumor selectivity in both two-dimensional cell and three-dimensional tumor sphere models.

It can efficiently trigger ICD at sub-IC50 concentrations and reshape the tumor immune microenvironment by releasing three key damage-related molecular patterns: inducing rapid extracellular release of ATP, recruiting and activating antigen-presenting cells. It promotes the translocation of calreticulin from endoplasmic reticulum to cell membrane and transmits 'phagocytosis signal' to improve the efficiency of antigen uptake. It promotes the release of HMGB1 (High Mobility Group Box 1) in the nucleus and promotes the maturation of antigen-presenting cells through RAGE (Receptor for Advanced Glycation Endproducts) and TLR (Toll-Like Receptor) pathways. Under the synergistic effect of direct killing and ICD immune activation, tumor-associated antigens are effectively presented, cytotoxic T cells are induced to proliferate and activate, specific anti-tumor immunity and long-term immune memory are established, and tumor growth, invasion and metastasis are inhibited. Among them, LMB033 has better light control efficiency and ICD induction ability, and its application potential is outstanding.

In order to enhance the synergistic effect, the structure of the active peptide can be optimized by molecular modification to improve the light-controlled selectivity and membrane binding ability ; relying on light-controlled activation to achieve precise local administration of tumor and prolong the effective concentration; combined with immune checkpoint inhibitors to relieve T cell exhaustion and enhance immune response ; the nano-delivery carrier is used to improve the stability of peptides and tumor penetration ability, so as to ensure the continuous release of ICD signals [10]. Multi-strategy synergy can further amplify the killing and immune activation effects of peptide drugs, providing an efficient and safe new path for tumor-targeted immunotherapy.

5. Present Problems and Future Development Trends

In summary, bacitracin S and its light-controlled derivatives LMB002 and LMB033 can exert anti-tumor effects by inducing immunogenic cell death of tumor cells. They have the advantages of light-controlled targeting and can reduce non-specific tissue damage of drugs. They have good application prospects in precise immunotherapy of tumors. However, there are still obvious limitations in the overall research of this series of active peptides: there is no uniform standard for drug preparation and purification process, and the batch quality stability is insufficient; the pharmacokinetic data in vivo are missing, and there is no basis for the design of drug delivery scheme. The research only stays in the in vitro model, and there are obvious faults in the in vivo drug research. The ICD immune regulation pathway and the mechanism of drug-immune cell interaction are not yet clear, and the overall research is difficult to support the follow-up drug development and clinical transformation.

Looking at the overall development trend in the field, combined with the relevant research progress in recent years, it can be seen that tumor treatment has gradually shifted from direct killing of tumor cells to immunogenic death-mediated systemic anti-tumor immune activation mode. Compared with traditional chemotherapy drugs, polypeptide drugs have low toxicity and good biocompatibility. Combined with light-controlled space-time precise control technology, polypeptide drugs can effectively solve the industry pain points of poor targeting and obvious systemic toxic and side effects of anti-tumor drugs, which has become a hot direction of research and development of new anti-tumor drugs. At the same time, the existing research gradually focuses on the two core directions of ICD key molecular regulation network analysis and in vivo druggability evaluation of polypeptide drugs and pays more attention to the standardized development of the whole chain of drugs and the mining of the immune interaction mechanism of tumor microenvironment. Relying on the above industry development direction, light-controlled ICD anti-tumor active peptides still have broad research and development space and will also become an important research branch in the field of precision tumor immunotherapy in the future.

6. Conclusion

In this study, the active peptide has the dual effects of direct tumor suppression and bidirectional immune regulation. It can not only destroy the structure of tumor cells, block proliferation and metastasis, but also fully activate immune cells and balance cytokine levels. Taking brevipeptide S and its light-controlled derivatives as an example, it was clarified that active peptides can induce tumor immunogenic cell death, release damage-related molecules to activate antigen-presenting cells and produce long-term anti-tumor immune memory. At the same time, four synergistic strategies of molecular modification, light-controlled administration, combined immunosuppressive agents, and nanocarriers were summarized.

For immunotherapy, there are problems such as immunosuppression, obvious toxic and side effects, and unclear mechanism of active peptides. This study completely analyzes the internal mechanism of active peptides synergistic immunotherapy and confirms that functional foods rich in active peptides are safe tumor-assisted intervention resources, providing a theoretical basis for peptide-assisted anti-tumor product development and clinical transformation. The existing related

research only stays in the in vitro model and lacks complete pharmacological data and unified preparation standards in vivo. Future research will conduct in-depth analysis of the ICD regulatory pathway, strengthen studies on the in vivo druggability of peptides, establish a standardized production and delivery system, and advance the clinical application of active peptide functional foods combined with immunotherapy.

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