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Thermalization of Cold Tumor: A Comprehensive Treatment Path for the Transformation of Cold Tumor to Hot Tumor

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Abstract:

This article reviews the emerging comprehensive treatment strategies for the transformation of "cold tumor" to "hot tumor", aiming to overcome the limitations of immunotherapy in tumors with low response rates. "Hot tumors" usually have abundant immune cell infiltration and active immune microenvironment, while "cold tumors" respond poorly to immunotherapy due to less immune cell infiltration and strong inhibitory microenvironment. This article focuses on three TME remodeling strategies: Tesla Cell activates innate immunity through metabolic reprogramming (such as inhibition of LDH-A and neutralization of lactate); Near-infrared photoimmunotherapy (NIR- PIT) uses photosensitizers to induce immunogenic death and reverse the immunosuppressive microenvironment. Hyperthermia enhances the activity of immune cells by directly killing tumor cells with high temperature and releasing antigens. In addition, this article analyzes the potential of these strategies in combination with immune checkpoint inhibitors, adoptive cell therapy and tumor vaccines, and compares their intrinsic/exogenous characteristics, safety and clinical transformation prospects. The "hyperthermia" of cold tumors provides a new direction for immunotherapy, which is expected to significantly improve the efficacy of refractory tumors.

Keywords:- cold tumor; hot tumor; thermalization of cold tumor; tumor microenvironment; immunotherapy

I. Introduction

China has one of the highest cancer burdens in the world. According to the 2022 data, the number of new cancer cases and deaths in China accounted for 24.17% and 26.44% of the world, respectively, of

which five high-mortality tumors such as lung cancer and liver cancer accounted for more than 67% [1]. Although immunotherapy has shown durable efficacy in some patients, the overall response rate is less than 30%, and it faces challenges such as high cost, immune-related toxicity and drug resistance.

Among them, the efficacy of immunotherapy for "cold tumors" is more limited. In such tumors, immune cells are difficult to infiltrate, the accessibility of targets is low, and there is metabolic competition (such as lactic acid accumulation) and interference of immunosuppressive cells, leading to treatment failure [2].

"Hot tumors" usually have abundant immune cell infiltration and active immune microenvironment, while "cold tumors" respond poorly to immunotherapy due to less immune cell infiltration and strong inhibitory microenvironment. The core of the resistance of "cold tumor" lies in the complexity of its immunosuppressive microenvironment (TME), including metabolic abnormalities (such as Warburg effect), immune cell dysfunction and physical barriers (such as binding site barrier). Existing strategies such as immune checkpoint inhibitor (ICI) monotherapy have a low response rate to "cold tumor", and there is an urgent need to break immune tolerance through TME remodeling [3].

This article reviews the similarities and differences in mechanism and clinical potential of three emerging TME remodeling strategies -- Tesla Cell, near-infrared light immunotherapy (NIR-PIT) and hyperthermia, focusing on how they achieve "cold and heat conversion" through metabolic reprogramming, immunogenic death (ICD) induction or physical energy input. The intrinsic/exogenous characteristics, safety and transformation potential of the three emerging TME remodeling strategies were compared. The prospect of systemic anti-tumor immunity after hyperthermia of cold tumors combined with a variety of immunotherapies, such as ICIs, adoptive immunotherapy (ACT) and tumor vaccines, is discussed, which provides a new direction for the treatment of "cold tumors".

II. Cold tumor and hot tumor

Cold tumors and hot tumors are classified according to the infiltration of immune cells and the activity of immune response in the tumor microenvironment (TME) [4].

There are a large number of immune cells infiltration in the TME of hot tumors, especially effector T cells are highly enriched, and these immune cells are in an activated state and can actively recognize and attack tumor cells. Such tumors are usually highly immunogenic, meaning that they are more effective in eliciting the body's immune response.

The TME of cold tumors has less infiltration of immune cells and an inactive immune response. The immune microenvironment of cold tumors is usually characterized by low or no expression of PD-L1, inactivation of the interferon pathway, and defective antigen presentation. The formation of cold tumors is related to a variety of factors, including low immunogenicity of tumor cells, more immunosuppressive cells (such as regulatory T cells (Tregs), tumor- associated macrophages, etc.) in TME, deposition of tumor extracellular matrix, and hypoxia.

Hot tumors have a good response to immunotherapy (such as ICIs), while cold tumors need to enhance the infiltration and activity of immune cells by means of TME remodeling, so as to improve the effect of immunotherapy.

III. Emerging TME remodeling strategies

A. Tesla Cell

The "charging" process of cell battery is a symbol of the restart of the tumor-immune cycle. Its core goal is to transform the "cold tumor" with less immune cell infiltration and unfavorable immune microenvironment into the "hot tumor" with rich immune cell infiltration and active immune response, so as to create more favorable conditions and lay a more solid foundation for immunotherapy [5].

In the process of "charging" the cell battery, the application of cGMP and STING agonists can significantly improve the sensing ability of the innate immune system. This improvement helps to break the immunosuppressive state of the "cold tumor" and promote its transformation into a "hot tumor", thereby enhancing the overall efficacy of immunotherapy.

In TME, low oxygen conditions prompt T rely on glycolysis to maintain cell proliferation and function, but "warburg effect" of the tumor cells can produce a large amount of lactic acid, quickly glucose and cause metabolic stress to T cells, inhibit the glycolysis ability and IFN - gamma, lead to immunosuppression and ICIs resistance. In addition, cancer-associated fibroblasts (CAF) and tumor-associated macrophages (Tams) further promote lactate accumulation through the "reverse Warburg effect", which aggravates immunosuppression. Through metabolic reprogramming, the cell battery inhibits lactate dehydrogenase A (LDH-A) to reduce lactate production and restore the normal pH of the microenvironment, thereby promoting the differentiation of monocytes into dendritic cells (DC), enhancing antigen presentation and T-cell activation. Combined with sodium bicarbonate to neutralize tumor acidity and ICI

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or adoptive cell therapy, it can effectively promote T cell infiltration, improve anti-tumor response, and promote the transformation of tumors from “cold” to “hot”.

B. NIR-PIT

NIR-PIT can achieve precise targeting by coupling photosensitizers (such as IRDye700DX) with tumor-specific antibodies, and near-infrared light irradiation can trigger a triple synergistic anti-tumor effect [6].

The core mechanism of this technology includes three aspects: first, the direct phototoxic effect, the near-infrared light triggers the photosensitizer, which leads to the destruction of cell membrane structure and rapid death; The second is to activate the systemic immune response. Dead cancer cells release antigens to promote the maturation of DCs and activate T cells, thereby producing long-lasting anti-tumor immune memory and inhibiting the growth of distant metastases. The third is TME reprogramming and “cold tumor hyperthermia”.

NIR-PIT can transform “cold tumor” into “hot tumor” through the following mechanisms: After ICD induction and photoactivation, calreticulin (CRT) was exposed on the surface of tumor cells, and damp- associated molecular patterns (DAMPs) such as HMGB1 and ATP were released, forming a strong “eat-me” signal, which increased the antigen presentation efficiency of DCs by 3-5 times and significantly enhanced T cell activation. The immunosuppressive microenvironment was reversed, and NIR-PIT selectively eliminated M2 tumor-associated macrophages (TAMs), promoted the secretion of pro-inflammatory factors (such as IL-6 and TNF-α), reduced the proportion of Tregs, and reshaped the immune-supportive microenvironment. The density of CD8+ T cells in tumor tissue increased 8-10 times within 72 hours after treatment, accompanied by the down-regulation of PD-1/PD-L1 signaling pathway, forming a long-lasting immune surveillance effect.

ICD is one of the core mechanisms of NIR-PIT, which can be divided into three steps to activate systemic anti-tumor immunity: calreticulin (CRT) exposure. After photoactivation, tumor cell membrane rupture leads to the transfer of CRT from the endoplasmic reticulum to the cell surface and promotes the phagocytosis of DCs as an “eat-me” signal. Damp-associated molecular patterns (DAMPs), including HMGB1 and ATP, are released. HMGB1 activates DCs through TLR4 signal, and ATP recruit more antigen-presenting cells to TME. Type I interferon pathway activation: Light-induced DNA damage can trigger the cGAS-STING pathway, promote the secretion of type I interferon, and further enhance T cell cross-activation [7]. in high mutation load tumors such as melanoma, ICD release are more likely to be T cell antigen recognition, strong immune response; In tumors with low mutation burden (such as pancreatic cancer), it is necessary to combine neoantigen vaccines to supplement tumor-specific antigens and overcome the problem of antigen deficiency [8].

NIR-PIT also improves the drug delivery efficiency of TME. During treatment, light-induced necrosis of perivascular cells can enhance tumor vascular permeability and promote drug penetration (i.e., EPR effect). However, high affinity of antibodies may lead to excessive accumulation of drugs around blood vessels, which may affect the killing effect of deep tumors. Therefore, optimizing the selection of antibody (such as medium and low affinity antibodies) can improve the uniform distribution of drugs in the tumor and further improve the efficacy.

NIR-PIT has received FDA breakthrough designation in recurrent head and neck cancer (targeting EGFR) and malignant pleural mesothelioma (targeting CD44), with objective response rates (ORR) of 40-60%. abscopal effect has been observed after local treatment, suggesting systemic immune activation [9,10].

Compared with traditional methods such as radiotherapy and chemotherapy, NIR-PIT has the advantages of precise targeting, systemic immune activation, and low toxicity and side effects. Its unique ability to “warm the cold tumor” makes it a breakthrough potential for immunotherapy-resistant tumor types, such as low mutation burden tumors. In the future, with the development of new photosensitizers and targeted antibodies, this technology is expected to achieve breakthroughs in more cancer types, providing a safer and more effective solution for tumor treatment.

C. Hyperthermia

Hyperthermia produces high temperature to directly kill tumor cells, increase the sensitivity of other treatments by increasing blood flow and oxygen supply, regulate the immune system, and stimulate anti- tumor immune response [11].

The direct effects of hyperthermia on tumor cells are mainly reflected in its ability to cause tumor cell necrosis, reduce tumor burden, and reduce the production of immunosuppressive factors. Necrotic tumor cells will release a variety of substances, these substances can be used as antigens to stimulate the body’s immune system to produce an immune response, and then attack the tumor cells. At the same time, the heat produced by high temperature structure can destroy tumor cells, causing cell death and antigen release, eliminate some inhibitory immune cells, reduce its inhibitory cytokines, thus reduce the TME immunosuppressive state.

In addition, hyperthermia can also significantly improve the activity of immune effector cells. Han Feng et al. have shown that hyperthermia can up-regulate the expression of molecules such as B7 on the surface of tumor cells and activate cytotoxic T cells to recognize and kill tumor cells, which can improve the therapeutic effect of patients with advanced cervical cancer, improve immune function, and promote the reduction of tumor marker levels [12].

Although hyperthermia can promote anti-tumor immunity, the immune response induced by hyperthermia when used alone is usually insufficient to completely control tumors. Hyperthermia can induce apoptosis or necrosis of tumor cells, release tumor antigens into the blood circulation, which are recognized and captured by antigen- presenting cells (APCs), then presented to T cells and secreted cytokines, activate the differentiation of effector T cells, and gather around the ablation lesions to form immune cell-infiltrating TME. This process can transform immune "cold" tumors into immune "hot" tumors, thereby improving the efficacy of immunotherapy.

IV. Combination of thermalization of cold tumors and immunotherapy

Immunotherapy aims to restore innate anti-tumor immune responses and restore and maintain tumor-specific immune pathways. However, in hot tumors, immune cells are highly active and the microenvironment is densely infiltrated by a large number of T cells, and immunotherapy can play a better role.

A. Combined ICIs

Immune checkpoints are an important part of the immune system, and their main role is to prevent an overly strong immune response that can cause damage to healthy cells in the body. Immune checkpoints are activated when proteins on the surface of T cells bind to their corresponding ligands on tumor cells. This binding sends a stop signal to T cells, which in turn prevents the immune system from attacking cancer cells. At present, ICIs are widely used in clinical practice,such as PD-1/PD-L1, CTLA-4, LAG-3, etc.

After the thermolization of cold tumors, the number and activity of immune cells in the TME increase, and ICIs can play a more effective role, further enhancing the anti-tumor immune response. For example, hyperthermia can induce tumor cell necrosis, release tumor antigens, and activate the immune system, while ICIs can further enhance the activity and function of immune cells, so as to attack tumor cells more effectively [13]. Lyu et al. performed anti-PD-L1 combined with thermal ablation therapy on 33 patients with advanced hepatocellular carcinoma who failed sorafenib treatment and found that hyperthermia improved the efficacy with tolerated toxicity, increasing the response rate from 10% to 24% [14]. This trial demonstrates that relatively good median survival may be achieved with additional hyperthermia during anti-PD-1 therapy, which may provide a promising strategy for the treatment of advanced HCC.

B. Combined ACT

ACT is a therapeutic method that directly kills tumor cells or stimulates immune responses by transfusing autologous or allogeneic immunocompetent cells after activation or genetic modification in vitro [15].

The core of this technology is the selection of autologous or allogeneic lymphocytes with antitumor activity in vitro and the subsequent infusion of these cells back into a patient with cancer, often with the coinfusion of appropriate growth factors to promote the survival and proliferation of these cells. ACT has significant advantages from both a theoretical and practical perspective. Precisely selecting a small number of antitumor cells with the right properties can allow them to be massively expanded ex vivo for subsequent therapy. With the help of in vitro assays, the specific cell populations and their effector functions required for cancer regression can be identified, and then the selection of cell expansion can be targeted. In the laboratory setting, cells can be activated without the restraint of endogenous inhibitory factors in vivo, and thus can be induced to exhibit desired antitumor effector functions. In particular, it is crucial to intervene in the host before cell reinfusion to create the most suitable in vivo environment for the cells to play a role. This approach has been shown to be effective in the treatment of experimental animals and cancer patients [16]. A key challenge for ACT is its highly personalized therapeutic properties. It is difficult to fit into the current routine practice patterns of oncology and requires high laboratory expertise. Fundamentally, it requires an entirely new therapeutic agent to be tailored to each patient. This patient specificity makes commercialization of ACT difficult. Pharmaceutical and biotechnology companies generally prefer to develop standardized drugs that are readily available, easy to produce, and easy to store and administer. As a result, ACT may be better suited to be offered as a customized service rather than a pharmaceutical product in the traditional sense.

In the single use of adoptive cell therapy, solid tumors generally have a suppressive tumor immune microenvironment, which prevents adoptive immune cells from infiltrating the lesion, limiting the application of ACT. Changing TME through cold tumor thermisation pathway

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such as hyperthermia provides a new idea for improving the efficacy of ACI in solid tumors.

C. Combined Tumor Vaccine

Neoantigen vaccine and near-infrared immunotherapy (NIR-PIT) are two major breakthrough technologies in the field of tumor immunotherapy in recent years. Neoantigen vaccines activate the patient's own T cell response by targeting tumor-specific mutations, while NIR-PIT uses the combination of photosensitizers and antibodies to achieve precise tumor cell killing. The combination of these two therapies is expected to overcome the limitations of single therapy through synergistic effect and provide a new strategy for tumor treatment.

De novo antigen vaccines are designed based on the mutation spectrum of the patient's tumor. Tumor-specific mutations are identified by whole exome sequencing and RNA sequencing, and their binding ability to the patient's HLA molecules is predicted. Studies have shown that de novo antigen vaccines can induce strong $CD4^+$ and $CD8^+$ T cell responses, and these responses are highly specific and can distinguish the mutant peptide from the wild-type peptide [17]. In melanoma patients, 60 percent of the immune peptides elicited $CD4^+$ and 16 percent elicited $CD8^+$ T cell responses after vaccination with the de novo antigen vaccine, and some patients even showed the ability to directly recognize their own tumor. In addition, the combination of the vaccine and PD-1 inhibitors can further expand the T-cell response spectrum and achieve complete tumor regression.

The combination of neoantigen vaccine and NIR-PIT may achieve synergistic effect through the following mechanisms: first, the antigen release and presentation are enhanced, and the ICD induced by NIR-PIT can release a large number of tumor antigens, providing more abundant targets for neoantigen vaccine and enhancing antigen presentation and T cell activation [18]. Secondly, the immune microenvironment is reshaped. NIR-PIT can reduce the infiltration of immunosuppressive cells (such as Tregs) and improve TME, thereby enhancing the infiltration and function of vaccine-induced T cells. The combination of neoantigen vaccine targeting a variety of mutations and NIR-PIT eliminating antigen-positive tumor cells may reduce immune escape.

The combination therapy of neoantigen vaccine and NIR-PIT represents an innovative direction of tumor immunotherapy, which is expected to achieve better clinical effects by activating specific immune responses and precise killing of tumor cells. Future research needs to focus on optimizing the combination regimen, exploring biomarkers, and conducting large-scale clinical trials to verify its safety and efficacy.

V. Comparison of three treatment pathways

A. Endogenous Immune Activation VS Exogenous AIDS

Table 1 summarizes the mechanisms of action, endogenous or exogenous characteristics, and their key dependent factors of the four tumor treatment strategies. Endogenous immune activation strategies (such as cell metabolic reprogramming) mainly play a role by regulating the metabolic state and immune cell function in TME, which rely on exogenous drugs (such as cAMP/STING agonists) to achieve. And exogenous means (such as NIR - PIT and heat) is dependent on the physical energy input or photosensitizer, the effect being limited by the factors such as target antigen expression or temperature control. In addition, combined strategies (e.g., hyperthermia +ICI) achieve synergistic effects by combining endogenous antigen release with exogenous immune regulation.

TABLE I.

TABLE I. Comparative analysis of endogenous immune activation and exogenous adjuvants

Strategies	Mechanics	Endogenous/exogenous	Key dependent factors
Cell battery "charging"	Activation of innate immunity by cAMP/STING agonists, metabolic reprogramming (e.gLDH-A inhibition, lactate neutralization)	Endogenous predominant (exogenous drugs required)	TME metabolic status and immune cell function
NIR-PIT	Nir light activates antibody- photosensitizer complexes, triggering immunogenic death and local immune responses	Exogenous (photosensitizer + light)	Target antigen expression, depth of light penetration

Hyperthermia	Hyperthermia directly kills tumor cells, releases antigens, and upregulates HSP and immune cell activity	Exogenous (physical energy input)	Temperature control, tumor site accessibility
Hyperthermia +ICIs	Hyperthermia provides antigen, ICI relieves T-cell suppression	Internal and external binding	Synergistic signaling (antigen +PD- 1/CTLA-4 inhibition)
Hyperthermia +ACT	Hyperthermia improves TME and promotes adoptive T-cell infiltration	Exogenous dominance	T cell expansion capacity and local effect on hyperthermia

B. Comparison of Safety, Controllability and Clinical Transformation Potential

Table 2 compares the safety, controllability, and clinical translational potential of different oncologic treatment strategies. Metabolic reprogramming of cells (“ recharging the cell battery “) and local hyperthermia have shown favorable safety profiles, whereas combination therapies such as hyperthermia plus adoptive cell therapy are associated with higher risks. NIR-PIT has the best controllability, but hyperthermia +ICI requires more precise dose regulation. In terms of clinical transformation, hyperthermia (alone or combined with ICI) has a good application basis, while adoptive cell therapy still needs more clinical verification. These differences suggest that the clinical application of different treatment strategies should be selected according to the specific conditions and treatment conditions.

TABLE II. Analysis of safety, controllability, and clinical translational potential of therapeutic strategies

Strategies	Security	Controllability	Clinical translational potential
Cell battery “recharging”	Higher (metabolizing drugs to avoid systemic toxicity, such as acidosis)	Medium (dependent on TME response)	High (can be combined with existing immunotherapies)
NIR-PIT	Medium (photosensitizer may cause photosensitivity; Precise targeting is required)	High (controllable light range)	Medium high (has been partially approved, needs to optimize the target)
Hyperthermia (alone)	High (local hyperthermia has few side effects and systemic hyperthermia has high risk)	Medium (temperature uniformity challenge)	High (mature technology and widely available)
Hyperthermia +ICI	Medium (may trigger immune hyperactivation, such as cytokine storm)	Medium (need to balance hyperthermia and ICI dose)	High (clinically available combination trials)
Hyperthermia +ACT	Low (adoptive cells may trigger an autoimmune response or CRS)	Low (complex cell preparation and large individual differences)	Medium (solid tumors to be proven)

VI. Conclusions

This article systematically analyzes the comprehensive treatment strategy for the transformation of “cold tumor” to “hot tumor”, focusing on three key methods: Near-infrared light immunotherapy (NIR- PIT) uses photosensitizers to induce immunogenic death and enhance T Cell infiltration. Hyperthermia destroys tumor cells with high temperature and releases antigens to improve the immune microenvironment. The results show that these strategies can effectively reverse the immunosuppressive state of tumors and significantly improve the response rate of immunotherapy, especially when combined with ICIs, adoptive cell therapy or tumor vaccines, which can synergistically enhance the anti-tumor immune response. For example, the addition of a PD-L1 inhibitor to hyperthermia increased the objective response rate in patients with advanced liver cancer from 10% to 24%. These findings provide new intervention directions for tumors that are refractory to traditional immunotherapy (e.g., pancreatic cancer, low-mutation burden tumors), and some therapies (e.g., NIR-PIT) have received FDA breakthrough designa-

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tion. However, this field still faces challenges such as toxicity of metabolic drugs, insufficient targeting precision, and the safety of combination therapy. Future studies need to optimize biomarker screening, explore more controllable combination regimens, and verify long-term efficacy through large-scale clinical trials, so as to promote the clinical transformation of cold tumor "heating" strategy, and ultimately improve the treatment outcomes of cancer patients.

VII. Authors Contribution

All the authors contributed equally and their names were listed in alphabetical order.

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