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Combinatorial immunotherapy and nanoparticle mediated hyperthermia☆

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ABSTRACT

Immune checkpoint therapy has become the first widely adopted immunotherapy for patients with late stage malignant melanoma, with potential for a wide range of cancers. While some patients can experience long term disease remission, this is limited only to a subset of patients and tumor types. The path forward to expand this therapy to more patients and tumor types is currently thought to be combinatorial treatments, the combination of immunotherapy with other treatments. In this review, the combinatorial approach of immune checkpoint therapy combined with nanoparticle-assisted localized hyperthermia is discussed, starting with an overview of the different nanoparticle hyperthermia approaches in development, an overview of the state of immune checkpoint therapy, recent reports of immune checkpoint therapy and nanoparticle-assisted hyperthermia in a combinatorial approach, and finally a discussion of future research topics and areas to be explored in this new combinatorial approach to cancer treatment.

Contents

1. Introduction

Immune checkpoint (ICP) therapy [1] has become the first widely adopted and successful immunotherapy for the treatment of metastatic melanoma (MM) and holds great promise for achieving success in a broad range of cancers [2]. In contrast to direct cytotoxic approaches (e.g. chemotherapy, radiation, targeted therapies) that seek to directly kill cancer cells, immunotherapies alter the immune response so that the innate and adaptive systems attack and eradicate the cancer on its own, including induction of a long-term immunity. The first ICP therapy (ipilimumab), which was FDA approved in 2011, demonstrated the use of the first drug ever to significantly improve overall survival benefit in patients with MM. Most importantly, a subset of patients considered "complete responders" (~20%) experienced total tumor remission that included a long term response, remaining cancer free beyond 10 years [3,4]. In 2014, the FDA approved another set of ICP therapies (nivolumab and pembrolizumab) for patients with MM that increased durable

Abbreviations: ICP, immune checkpoint; MM, metastatic melanoma; NPHT, nanoparticle-assisted hyperthermia; NIR, near-infrared; AMF, alternating magnetic field; PTT, photothermal therapy; MFH, magnetic field hyperthermia; RFH, radiofrequency hyperthermia.

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response rates to 40% [5–7]. ICP therapies have been the most promising therapeutic to affect MM since the beginning of cancer treatment. In the coming years, we are likely to see additional immunotherapy approaches reach mainstream use, including adoptive T cell transfer, chimeric antigen receptor T cell therapy (CAR-T), and cancer vaccines [8].

The principle of ICP therapy is based on the expression of proteins on cancer cells that bind checkpoint proteins expressed on T cells. These checkpoint proteins function as "off switches" that inhibit T cell receptor mediated killing of a foreign body. Immune checkpoint inhibitors are antibodies that bind either of the checkpoint proteins on the cancer cell (e.g. PD-L1) or on the T cell (e.g. PD-1 or CTLA-4), allowing T cells to attack and kill cancer cells. The key challenges with current ICP therapy are low patient response rate and the potential for high toxicity [1]. While the reasons for low response rates are not completely understood, the current understanding is that tumors produce numerous immunosuppressive factors creating a "nonimmunogenic" tumor microenvironment. Immunogenic tumors are more likely to respond to ICP therapy as the tumor microenvironment is conducive to tumor cell recognition, containing infiltrating T cells, cytokines such as granzyme B, and memory T cell markers such as CD45RO and PD-L1 [1,9]. A single therapeutic approach will not overcome the numerous, dynamic and evasive immune strategies of the tumor. The path forward is believed to be combinatorial approaches that convert a nonimmunogenic ("cold") tumor to an immunogenic ("hot") tumor that will respond to ICP therapy [1,10].

The advent of ICP has led to the investigation of combinatorial clinical treatment strategies combining ICP with well-established treatment approaches, such as radiation [11], chemotherapy [12], oncolytic viral therapy, and targeted therapy [13]. While improvements in treatment outcomes have been observed, there is no rationale or guidance for selecting the best combinatorial approach for an individual patient. This stems from the lack of techniques to monitor the dynamic immune response and a poor understanding of the specific impact of each combinatorial approach on the tumor microenvironment. Importantly, these approaches exhibit significant toxicity (chemotherapy, targeted therapy) and/or disease resistance (chemotherapy, radiation). Therefore, a continued unmet need exists for combinatorial therapies that can enhance ICP therapy with limited toxicity profiles and an understanding of the synergy involved in the combinatorial approaches.

Nanoparticle-assisted hyperthermia (NPHT) with ICP therapy has emerged as a potential combinatorial cancer treatment approach. NPHT involves administration of nanoparticle (NP) platforms targeted to the tumor site, followed by irradiation with an external energy source to produce heat and localized hyperthermia. An overview of this approach is outlined in Fig. 1. The primary advantage of NPHT is the ability to perform well-controlled, targeted volumetric heating specific to tumors. In fact, localized heating provides a relatively benign, low toxicity, outpatient treatment when compared to the systemic toxicity issues associated with molecular targeted therapies (e.g. MEK inhibitors) or chemotherapy and has the potential to open up immunotherapies to a larger population. To date, the vast majority of the research and development of this approach has been directed toward eradication of primary tumors, and many studies have shown the success of NPHT in debulking tumors in preclinical models [14–16]. Several clinical trials have been conducted or are underway utilizing near-infrared (NIR) laser irradiation of gold based nanoparticles [17,18] and alternating magnetic field (AMF) irradiation of magnetic nanoparticles [19].

While successful in debulking primary tumors, NPHT does not generally address the treatment of metastatic disease, which is responsible for the vast majority of cancer deaths. However, the hyperthermia community has long recognized and documented the systemic immune response due to local hyperthermia, highlighting the opportunity for combining these immune modulatory responses with immunotherapy strategies to treat metastatic disease. Since the late 1990s, several groups have shown enhanced systemic responses of NPHT when used with immune adjuvant treatments [20]. Since ICP therapies are now approved as standalone, first-line treatments for patients with advanced melanoma, combining ICP therapy with NPHT offers a new opportunity

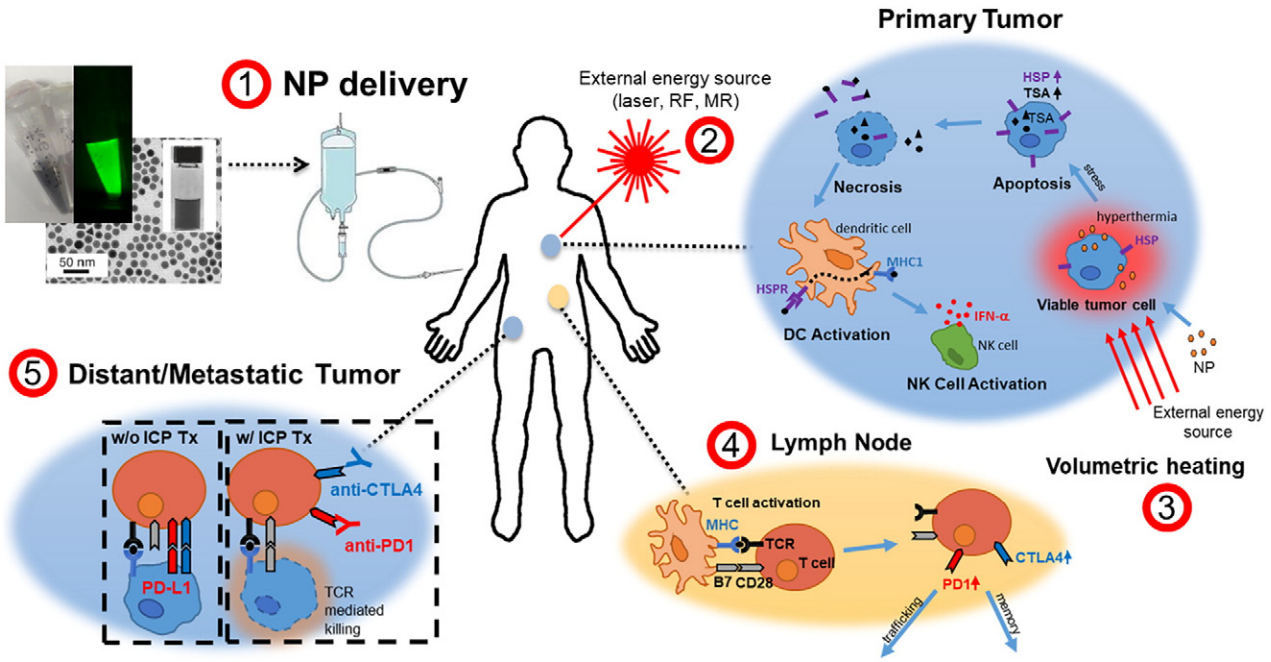

Fig. 1. Combinatorial NPHT and ICP therapy. 1) Systemic administration of nanoparticles that localize to the tumor and 2) irradiation with an external energy source are the main components of NPHT. 3) Tumor hyperthermia initiates the apoptosis responses that upregulate tumor specific antigens (TSA) and expression of heat shock proteins (HSP). Necrosis releases TSA and HSP-TSA complexes that activate antigen presenting dendritic cells (DC). HSP receptors (HSPR) on DCs recognize HSP-TSA complexes, activating natural killer (NK) effector cells and release of cytokines and chemokines. 4) DCs traffic TSA to the lymph nodes (LN) where they activate T cells with T cell receptors (TCR) specific to the TSA. Activated T cells upregulate inhibitory surface receptors (PD-1 and CTLA-4), and 5) traffic back to the primary and distant/metastatic tumors throughout the body, initiating TCR mediated killing of tumor cells. In the absence of ICP therapy, inhibitory ligands on the tumor cells (e.g. PD-L1) would down-regulate and inhibit a full response; however, blocking the immune checkpoints allows for a full, uninhibited immune response, ultimately resulting in tumor cell killing and immune memory.