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Recent advances in targeted nanoparticles drug delivery to melanoma☆

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Abstract

Melanoma is one of the most aggressive skin cancers, notorious for its high multidrug resistance and low survival rate. Conventional therapies approved by the FDA for melanoma treatment (e.g., dacarbazine, interferon-alpha-2b and interleukin-2) are limited by low response rate and demonstrate no overall survival benefit. Novel targeted therapies (e.g., vemurafenib, dabrafenib, and trametinib) have higher initial response rate and clear impact on the overall survival, but relapse usually occurs within 6 to 9 months. Although immunotherapy (e.g., ipilimumab) can achieve long-term and durable response, rate of adverse events is extremely high. With the development of nanotechnology, the applications of nanocarriers are widely expected to change the landscape of melanoma therapy for foreseeable future. In this review, we will relate recent advances in the application of multifunctional nanocarriers for targeted drug delivery to melanoma, in melanoma nanotheranostics and combination therapy, and nanopharmaceutical associated melanoma clinical trials, followed by challenges and perspectives.

Key words: Nanoparticles; Melanoma; Drug delivery; Targeting; Nanotheranostics

Introduction

Melanoma, originated from the malignant transformation of melanocytes, is one of the most aggressive skin cancers, notorious for its high multidrug resistance (MDR), easy to relapse and low survival rate. Nearly 76,100 newly diagnosed cases of melanoma were reported in the United States in 2014 with an estimated 9710 expected deaths.[1] The statistical data collected from the National Cancer Institute of America quote melanoma as the fifth and seventh most commonly diagnosed malignancies among men and women, respectively.[2] The median survival time for metastatic melanoma patients is about 8-9 months with a 3-year overall survival rate of less than 15%.[3]

As a highly heterogeneous malignancy, melanoma resulted from the interplay of genetic, host, and environmental factors.[4] The mutations of oncogenes and tumor suppressors thought to be the drivers of melanomagenesis include BRAF (~50% mutation frequency), NRAS (~30%), KIT (~1%), p53 (~5%), PTEN (~50%) and so on.[4] Furthermore, the higher somatic mutation load in melanoma than in other cancer types is believed to be attributable to the preponderance of cytosine-to-thymine nucleotide substitutions as a result of UV radiation exposure.[5] Also, melanoma is one of the most immunogenic tumors in which immune evasion and immune suppression play an important role.[6] The abnormal and down-regulated expression of MHC-I molecules on melanoma cell surface was due to the loss of transporters associated with antigen processing (TAP) function and loss of β_2m within the endoplasmic reticulum, which resulted in the loss of recognition by tumor infiltrated T lymphocytes (TILs).[7] Up-regulation of programmed death ligand-1 (PD-L1) expression on the surface of melanoma cells led to the loss of effector function of TILs.[8] Also myeloid-derived suppressor cells (MDSCs) such as tumor associated

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macrophages (TAM) as well as the suppressive tumor microenvironment repress the host immune responses and promote the tumorigenesis.[9,10]

Surgery offers a good chance of recovery at the early stage of melanoma. However, for advanced metastatic melanoma, only modest results are obtained with DTIC (1975), recombinant interferon α-2b (1995) and high-dose interleukin 2 (HD IL-2) (1998), the only three conventional therapeutic agents approved by the Food and Drug Administration (FDA) for metastatic melanoma.[11–13] All of these drugs are limited by low response rates (~15%) and show no clear impact on the overall survival, followed by severe toxicity.[11–13]

Small targeted molecules such as selective mutant $BRAF^{V600E}$ inhibitors vemurafenib (2011) and dabrafenib (2013), MEK inhibitor trametinib (2013),[14,15] and immune checkpoint inhibitor ipilimumab (2011), an anti-cytotoxic T lymphocyte-associated antigen-4 (anti-CTLA-4) monoclonal antibody,[16] which have been newly approved by the FDA, marked a major breakthrough in clinical metastatic melanoma treatment. Although improved clinical response rate, clear benefits of progression-free survival (PFS) and the overall survival have been achieved by the clinical application of these novel therapeutic agents, some long-term obstacles and major challenges in melanoma therapy still need to be conquered. First of all, although many chemotherapeutic agents (e.g., nitrosoreas, vinca alkaloids and taxanes, platinums, etc.) are potentially effective anti-melanoma drugs with comparable response rate to that of DTIC, poor solubility and/or stability as well as serious toxicity limit their applications in clinical melanoma treatment. Thus, how to improve the pharmaceutical and pharmacological properties of these chemotherapeutic agents without changing the drug molecules is of great concern. Secondly, how to deliver these chemotherapeutics more efficiently to tumor tissues and further increase the efficacy of these agents by enhancing the intracellular concentrations in melanoma cells? Thirdly, how to exert melanoma killing effect while monitoring the biodistribution of the therapeutic agents but with smaller systemic dosing and less administration frequency? Last but not least, how to make a rational combination plan to overcome the resistance caused by single drug usage?

Fortunately, the development of nanotechnology and the application of nanocarriers in medicine make it possible to get over the above mentioned hurdles. For example, multifunctional nanoparticles (NPs) have been developed to elongate the circulation time and improve the accumulation of drugs in the tumor tissues based on the surface modification (e.g., PEGylation) and enhanced permeation and retention (EPR) effect, to enhance the uptake of the drugs by tumor cells and avoid the adverse effect through both specific and enhanced interactions between the targeted tumors cells and ligand-modified NPs, and to overcome MDR by co-encapsulating rational combination of different therapeutic agents. Furthermore, nanotheranostics, by incorporation of therapeutic and diagnostic agents in the same NP, is a brand new protocol with the capability of detecting while treating tumors simultaneously. Besides all these opportunities and advantages, the challenges are not insignificant. For example, the complexicity of the EPR effect due to the interpatient variability and tumor heterogeneity will have great influence on the efficacy of both passive and active targeting. And the difficulties in achieving reproducible and controlled synthesis of NPs, lack of universal standard for evaluating the potent cytotoxicity of NPs and surfactants etc, are unavoidable problems before the NPs reach commercialization. Only by minimizing these pitfalls can we see the most immediate clinical translation. In this review, we will mainly focus on the targeted drug delivery to melanoma, associated theranostic strategies and combination therapy, and nanopharmaceutical associated melanoma clinical trials, followed by the current status, challenges and perspectives of this field.

Targeted NPs drug delivery to melanoma

Targeting in nanotechnology refers to the spatial localization of the NP within the intentional sites and is distinct from molecularly targeted drugs. Targeted drug means blocking essential biochemical pathways or mutant proteins that are required for tumor cell growth.[17,18] The aforementioned vemurafenib and dafrafenib are targeted drugs for melanoma patients with mutant $BRAF^{V600E}$.[14] There are many other therapeutic drugs which can target different signaling pathways of melanoma such as KIT and extracellular regulated protein kinases (ERK) inhibitors.[4] By contrast, targeted drug delivery refers to the preferential accumulation of a drug within a target site that is independent of the method and route of drug administration.[17]

Targeted drug delivery to melanoma with the aid of nanocarriers allows therapeutic drugs to accumulate in tumor tissues with a high concentration, facilitates the uptake and internalization of the drug-loaded NPs by tumor cells, and avoids off-target distribution which may lead to severe adverse effects. In addition, the incorporation of therapeutic agents such as chemotherapeutic drugs, metals or magnetic particles, proteins, nucleic acids and vaccines, creates an ideal delivery system for the clinical treatment for metastatic melanoma.

The principles of drug targeting to tumors can be divided into three categories: passive targeting, active targeting and triggered drug delivery responsive to different internal/external stimuli. Passive targeting is based on the EPR effect, whereby the vasculature leakiness and poor lymphatic drainage of the tumors enable the drug-loaded NPs to accumulate in the tumor areas.[19] As opposed to passive targeting, active targeting refers to the specific interactions between the drug-loaded NPs and the targeted tumors by modifying the NPs with targeting ligands, such as antibodies, peptides, nucleic acid based ligands or small molecules, which specifically bind to the receptors or molecules highly expressed at the targeted site.[20] Active targeting thus enables an enhanced interaction between the NPs and targeted tumor lesions and an increased internalization of drugs through specific receptor-mediated endocytosis. Also, by combining bio-responsive NPs with internal or external stimuli (such as pH gradient, hyperthermia, alternating magnetic field, light and acoustic), stimuli-triggered drug release can be successfully achieved. These stimuli-responsive NPs are designed to only release the encapsulated therapeutic drugs upon applying locally confined triggers, thereby maximizing drug release at the pathological sites of tumors. Inorganic NPs, polymeric micelles,