

Review Article

Advances in biological treatment of melanoma

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ABSTRACT

Biological therapy involves the use of living organisms, substances derived from living organisms, or laboratory-produced versions of such substances to treat disease. Metastatic disease have a grave prognosis in comparison to early stage metastatic cancer where surgical treatment can benefit the patients thus traditional chemotherapy regimens have been found to offer relatively little survival benefit. Treatment of advanced or metastatic melanoma includes involvement of biological modalities such as immunotherapeutic approaches, targeted therapies and epigenetic modification therapies. The goal of immunotherapy for cancer is to provide an effective anticancer immune response. These biological therapies restore or increase the activities of specific immune-system components and counteract immunosuppressive signals produced by cancer cells. Monoclonal antibodies, are laboratory-produced antibodies that bind to specific antigens expressed by cells, such as a protein that is present on the surface of cancer cells but is absent from normal cells. They interfere with the action of proteins that are necessary for tumor growth. When bound to bevacizumab, VEGF cannot interact with its cellular receptor, preventing the signaling that leads to the growth of new blood vessels. MAb's that bind to cell surface growth factor receptors prevent the targeted receptors from sending their normal growth-promoting signals. The targeted therapeutic agents modulate specific pro-oncogenic mutations such as v-Raf murine sarcoma viral oncogene homolog B (BRAF), MEK inhibitors and CDK4/CDK6, PTEN and GNAQ/GNA11 genes. This review summarizes the biological agents and newer modalities of treatments, and their recent advancements and contributions in the treatment of patients with metastatic melanoma.

Keywords: Biological therapy, Metastatic melanoma, Targeted therapeutic agents

INTRODUCTION

Melanoma, develops in the cells (melanocytes) which produces melanin, it is the pigment that gives skin its color. Exposure to ultraviolet (UV) radiation from sunlight increases the risk of developing melanoma. It is the most serious type of dermatological malignancy.

It's prevalence has been documented to be increased amongst immunosuppressed transplant patients. Discoveries of frequent mutations involving BRAF(V600E), developmental and oncogenic roles for the microphthalmia associated transcription factor

(MITF) pathway, clinical efficacy of BRAF targeted small molecules, and emerging mechanisms underlying resistance to targeted therapeutics represent just a sample of the findings that have created a striking inflection in the quest for clinically meaningful progress in the melanoma field.¹

Cutaneous melanoma becomes more advanced when melanocytes undergo changes and it then becomes malignant. Melanoma is decreased incidence than basal cell and squamous cell carcinomas of skin, but is the most malignant dermatological malignancy. Interferon α -2 β (IFN α -2 β) and interleukin-2 (IL-2) have been

recently used as antineoplastic therapy which stimulates body's own immune response.

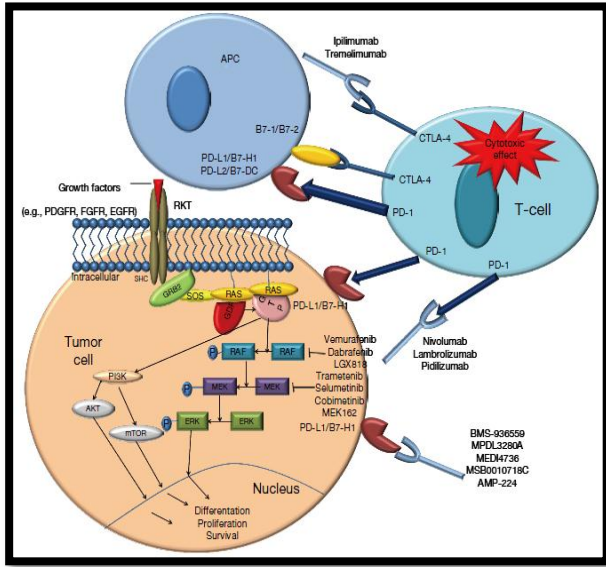


Figure 1: RAS-RAF-MEK-ERK signaling pathway.²

PATHOGENESIS OF MELANOMA

Pathogenesis of melanoma depends on DNA mutations which lead to the activation of oncogenes or to the inactivation of the tumor suppressor genes.

Best known intracellular signalling pathway is definitely the mitogen activated protein kinase (MAPK) pathway or RAS/RAF-MEK-ERK pathway (Figure 2).

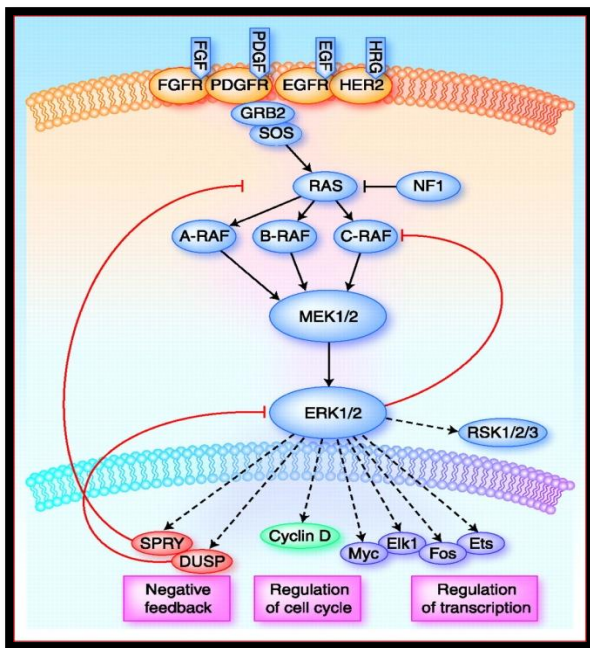


Figure 2: Interactions between immunotherapy and targeted therapy.³

On the surface of the cell there are transmembrane receptors which undergo signal transduction by growth factors such as EGF (epidermal growth factor), IGF (insulin-like growth factor), or TGF (transforming growth factor) this in turn leads to the activation of the RAS protein which transduces the signal to the group of serine-threonine kinases RAF, including ARAF, BRAF, and CRAF.

DNA methylation

DNA methylation is an important regulator of gene transcription. Hypermethylation, an epigenetic modification represses transcription of the promoter regions of tumor suppressor genes leading to gene silencing, this is under research.

miRNA

CpG island methylator phenotype predicts progression of malignant melanoma. Malignancy results as a result of methylation of multiple non coding, methylated-in-tumor (MINT) loci and sequential inactivation of tumor suppressor and tumor-related genes (TRG).

PTEN gene

Important tumor suppressor gene in melanoma is phosphatase and tensin homologue deleted from chromosome 10 (*PTEN*). Epigenetic *PTEN* silencing seems to be a relevant mechanism of inactivating this tumor suppressor gene in melanoma which promotes melanoma development by depression of the AKT pathway.

The role of immune regulation

Pathophysiology of melanoma is the immune regulation of T-cells. T-cells are covered with various receptors which are the target of antigen-presenting cells (APCs). The antigen presentation in turn leads to activation or inactivation of the T-cell. The activation of a T-cell occurs by two concurrent mechanisms which consist of antigen presentation by APCs to the T-cell receptor (TCR) and the expression (by APCs as well) of protein B7 which interacts with the T-cell CD28 receptor. If these two processes occur activation of the T-cell. Nevertheless, there are numerous pathways of inactivation of once activated T-cells. The phenomena mentioned above consist of (1) the expression of the CTLA-4 receptor on the surface of a T-cell, which after binding to the protein B7 on APCs transduces the inhibitory signal to the nucleus and (2) the expression of the PD-1 receptor on the T-cell surface which may lead to the inactivation of the T-cell after binding to the PD-L1 (programmed cell death 1 ligand) on tumor tissue. The inhibition or checkpoint blockade of CTLA-4 or PD-1 (or PD-L1) may thus be used as the target of the antitumor treatment (Figure 2).⁴⁻⁶

TARGETED THERAPY

Adoptive T-cell therapy (ACT)

Most treatments for patients with metastatic melanoma have a low rate of complete regression and thus overall survival in these patients is poor. Cell transfer therapy with autologous TILs thus can mediate durable complete responses in patients with metastatic melanoma and has similar efficacy irrespective of prior treatment.⁷

Oncolytic viral therapy (OV)

Oncolytic viruses (OV) selectively replicate and kill cancer cells and spread within the tumor, while not harming normal tissue. OV's encompass a broad diversity of DNA and RNA viruses that are naturally cancer selective or can be genetically engineered. Many aspects of the OV tumor/host interaction are important in delineating the effectiveness of therapy.

- Innate immune responses and the degree of inflammation induced;
- Types of virus induced cell death;
- Inherent tumor physiology, such as infiltrating and resident immune cells, vascularity/hypoxia, lymphatics, and stromal architecture; and
- Tumor cell phenotype, including alterations in IFN signaling, oncogenic pathways, cell surface immune markers [MHC, co stimulatory, and natural killer (NK) receptors], and the expression of immunosuppressive factors.⁸

BRAF inhibitors

Activating BRAF kinase mutations arise in 7% of all human tumors. Thus, it is important to establish molecular mechanisms underlying such resistance to develop effective therapeutic strategies to overcome or prevent drug resistance. Elevated CRAF protein levels account for the acquisition of resistance to AZ628 in these cells, associated with a switch from BRAF to CRAF dependency in tumor cells. Elevated CRAF protein levels may similarly contribute to primary insensitivity to RAF inhibition in a subset of BRAF mutant tumor cells.⁹

Targeted therapy can successfully block oncogenic signalling in BRAFV600-mutant melanoma with high initial clinical responses, but relapse rates are also high. However, it is becoming evident that the effects of paradoxical mitogen - activated protein kinase pathway activation by BRAF inhibitors in non *BRAF* mutant cells needs to be taken into account, which may be implicated in the problems encountered in the first clinical trial testing a combination of the BRAF inhibitor vemurafenib with ipilimumab (anti-CTLA4), with significant liver toxicities.¹⁰ BRAF^{V600E} is the most frequent oncogenic protein kinase mutation known. Furthermore, inhibitors targeting “active” protein kinases have demonstrated

significant utility in the therapeutic repertoire against cancer.¹¹

Vemurafenib

It is a BRAF V600 inhibitor, and when used for the treatment of metastatic melanoma (stage III and IV) and recurrent melanoma, can slow the progression of lesions.¹² It indicated as monotherapy for the treatment of adult patients with metastatic melanoma with for the BRAF V600 mutation.

Dabrafenib

Another BRAF inhibitor used for treatment of melanoma is dabrafenib. In the United States it was approved by the FDA in 2013 as a single-agent treatment for unresectable or metastatic melanoma with BRAF V600E mutation.^{13,14} The most common adverse effects included cutaneous squamous-cell carcinoma, fatigue, and pyrexia.

LGX818

Another BRAF inhibitor which is currently under development for BRAF-mutant melanoma is LGX818. The agent causes noticeably longer inhibition of the MAPK pathway when compared to vemurafenib or dabrafenib.¹⁵

Resistance to treatment

The potential mechanisms of resistance include intrinsic resistance or acquired resistance consisting of either ERK-dependent or non-ERK-dependent mechanism. The intrinsic resistance may be caused by several different abnormalities regarding the cell cycle regulation. The amplification in cyclin D1, which can be observed in 15–20% of BRAF mutant melanomas, is associated with a higher rate of resistance to BRAF inhibitors.^{16,17}

Another biomarker that can be used for predicting the probability of resistance to BRAF inhibitors is the status of the suppressor gene, PTEN. As it was reported, PTEN loss is associated with resistance to BRAF inhibitors.¹⁸ Another mechanism which plays the important role in resistance to BRAF inhibitors is the interaction between hepatocyte growth factor (HGF) and its receptor CMET.

MEK inhibitors

Trametinib

Trametinib, a highly selective MEK1/2 inhibitor, was approved by the FDA on May 29, 2013, as a firstline treatment for patients with unresectable or metastatic melanoma with V600E/K mutation.^{19,20} The most commonly observed adverse events during the treatment included rash, diarrhea, edema, hypertension, and fatigue. The events typical of MEK inhibitors that could be

noticed were chorioretinopathy (<1%) and the decrease of ejection fraction (7%).

Cobimetinib

Cobimetinib is a noncompetitive inhibitor, highly specific for MEK1 and 2 kinases developed by Exelixis and Genentech (Roche). It is used in combination with vemurafenib, a BRAF inhibitor, to treat melanoma.

MEK162

MEK162 is a highly selective MEK1/2 kinases inhibitor. The most commonly seen adverse events were acneiform dermatitis, rash, peripheral edema, facial edema, diarrhea, or elevated creatinine phosphokinase and serous retinopathy like events. MEK162 is the first agent to be active against NRAS-mutant melanoma.²¹

C-KIT inhibitors

C-KIT is a receptor tyrosine kinase which activates the MAPK signaling pathways resulting in proliferative and survival effects.

Nilotinib

Nilotinib may achieve disease control in patients with melanoma harboring KIT alterations and whose disease progressed after imatinib therapy.²²

Imatinib

Melanomas harbor aberrations in the c-Kit gene.²³ The first clinical evidence of the potential of this concept was observed by blocking the KIT gene, long known for its role in gastrointestinal tumors and chronic myeloid leukemia. A drug capable of inhibiting its activity has been developed: Imatinib.²⁴

IMMUNOTHERAPY

PD-1/PD-L1 immune checkpoint in cancer

Malignant tumors bear the potential of increased immunogenicity because of their high number of somatic mutations, depicting a mutational landscape extremely variable at the inter- and intra-patient level.²⁵⁻²⁷

Yadav and colleagues sought to simplify the discovery of such immunogenic mutant peptides by characterizing their properties.²⁸ Tumor mutations are useful reservoirs of exploitable neo-antigens. Castle et al analyzed the mutanome of the widely used B16 melanoma cell line and tested 50 MHC-binding m-peptides, 16 of which were immunogenic and 11 of which preferentially recognized the mutant peptide over the wild-type counterpart. Importantly, they showed that vaccination with 2 of those suppressed the growth of established B16 melanomas.²⁹

In a time of intense quest for personalized modalities for cancer therapy, immune interventions that aim at priming or boosting anti-tumor immune responses tailored to mutational heterogeneity holds much promise. Consistent with this concept, Gubin et al. employed genomics and bioinformatics approaches to identify tumor-specific mutant proteins as a class of T-cell rejection antigens following anti-PD-1 and/or anti-CTLA-4 therapy.³⁰

This has also been observed in a series of melanoma patients, where somatic neopeptides that elicited an antitumor response were augmented by and associated to clinical response to CTLA-4 blockade.³¹

CTLA-4 Antibodies

Ipilimumab

Ipilimumab is a fully human IgG1 monoclonal antibody that blocks cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), an immunosuppressive receptor on T cells.^{32,33} Grade III/IV immune-related adverse events (IRAE) including dermatitis, enterocolitis, and hypophysitis are usually seen amongst patients. The FDA recently approved ipilimumab for treatment of metastatic melanoma (stage III and IV) and recurrent melanoma in patients who had previously been treated with other chemotherapeutic agents.^{34,35}

Its mechanism of action is to fundamentally interfere with the process of antigen presentation (Figure 1). In this process, the antigen-presenting cell (APC) presents the antigen via the MHC.³⁶ T lymphocytes then receive this signal through a specific receptor. However, T-cell activation is dependent on co-stimulatory factors. An accessory stimulus is provided by the interaction of a cell surface protein called host B7, which binds to the CD-28 protein. Along with this process, it triggers a counterbalance system of immune activation, a kind of “brake”, which is exerted by CTLA-4.³⁷ Ipilimumab interacts with CTLA-4 to block this inhibitory activity, “releasing the brake” on activation. The immediate result is increased immune activation, allowing the immune system to recognize and attack malignant cells. It was approved by the FDA on March 25, 2011, to treat patients with unresectable or metastatic melanoma.³⁸

Tremelimumab

Tremelimumab is a CTLA-4 blocking antibody. Cytotoxic T lymphocytes (CTL) are able to recognize and destroy cancer cells. However, there is also an inhibitory mechanism (checkpoint) that blocks this destruction. Tremelimumab closes this inhibitory mechanism, allowing CTLs to continue to destroy cancer cells.³⁹

Tremelimumab binds to protein CTLA-4, which is expressed on the surface of activated T lymphocytes and inhibits cancer cell killing. Unlike Ipilimumab (another

human monoclonal antibody against CTLA-4), this is a IgG1, IgG2, tremelimumab is homologous.^{40,41}

PD-1 inhibitors

They include Nivolumab, Pembrolizumab/Lambrolizumab (MK-3475) and Pidilizumab. Nivolumab is a fully human monoclonal antibody against PD-1 (programmed death receptor-1). It has been approved by FDA recently (December 22nd 2014) to treat unresectable or metastatic melanoma with no response to other drugs.⁴² It is used as a first line treatment for inoperable or metastatic melanoma in combination with ipilimumab if the cancer does not have a mutation in BRAF and as a second-line treatment for inoperable or metastatic melanoma following treatment of ipilimumab and, if the cancer has a BRAF mutation, a BRAF inhibitor.^{43,44}

PD-L1 inhibitors

They include MPDL3280A, BMS-936559 and MEDI4736. MPDL3280A, a human monoclonal antibody against PD-L1, blocks the binding of PD-L1 to PD-1 and B7-protein. The treatment with MPDL3280A was well tolerated.⁴⁵ Currently, there are several studies in progress associated with MPDL3280A in melanoma.^{46,47}

CONCLUSION

Despite the spectacular success of the biological agents designed for treatment of melanoma, a problem of resistance to treatment is a major challenge for clinicians. A better understanding of the process of melanoma development and of the mutation profile of various genes has yielded knowledge that became the basis for development of new treatments.

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