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Review article

Towards therapeutic advances in melanoma management: An overview

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ABSTRACT

Melanoma is one of the most aggressive types of skin cancer with rapidly increasing incidence rate. The disease is largely considered incurable and the patients diagnosed with metastatic melanoma have a survival of not more than five years. Despite of the recent advances in anti-melanoma chemo- and immunotherapies, the available drugs are relatively toxic and responsive to only a limited subset of lesions. Currently, topical pharmacotherapy is demonstrated as an effective approach for the treatment of various skin cancers. Also, in vitro testing of melanoma cell lines and murine melanoma models has identified a number of relatively safe and effective phytochemicals. In this review, we described the use of topical pharmacotherapy for the treatment of skin cancers. Melanoma treatment by drugs targeting MAPK-pathway has also been discussed. Long non-coding RNAs and therapeutics targeting ER-associated pathways looks quite promising for the treatment of melanoma. Moreover, some natural anticancer compounds that have been reported to have anti-melanoma effects have also been described. At present a better understanding of genetics and epigenetics of initiation and progression of melanoma is needed for the identification of novel biomarkers and development of targeted therapeutics against melanoma.

Contents

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1. Introduction

Cancer, a genetic as well as an epigenetic disease, is driven by the accumulation of somatic mutations and reprogramming of epigenetic factors. These alterations ultimately lead to the activation of cancer causing oncogenes and inactivation of various genes involved in tumor suppression. One of the most common malignancies is the skin cancer with high incidence frequency in Caucasian population [1]. The primary cause of skin cancer is exposure to ultraviolet (UV) radiations. Skin cancer also occur either due to the defects in apoptotic pathways or abnormal increase and survival of the cells in epidermis [1]. Other major causative agents include human papillomavirus, tobacco consumption, chemical mutagens and genetic susceptibility [2]. Use of various immunosuppressive drugs such as azathioprine and cyclosporine A have also been found to increase the risk of skin cancer by about 60 and 200 times, respectively [3].

Skin cancer is mainly of three types, named on the basis of cell from which they arise and clinical behavior: basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and malignant melanoma. The first two types come under the category of non-melanocytic skin cancer. Basal cell carcinoma grows quite slowly and can damage the surrounding tissue, but not capable of spreading to distant areas [4]. On the hand, squamous cell carcinoma is capable of metastasis to other parts of body [4]. Malignant melanoma is the most aggressive form of skin cancer which develops from melanocytes, the cells that are responsible for the protection of keratinocytes by harmful UV radiations. Keratinocytes regulate the physiology of melanocytes by secreting specific paracrine acting factors [5]. These factors are responsible for stimulating ERK/MAP-Kinase signaling cascade which regulates the differentiation and proliferation of melanocytes [6]. Interestingly, hyper-activation of the ERK/MAP-Kinase pathway has been reported in 90% of the melanomas [6].

Incidence of melanoma is associated with UV-radiation induced genetic aberrations that lead to uncontrolled growth of melanocytes [7]. In addition to genetic aberrations, epigenetics also play an important role in melanoma development and progression. Several microRNAs (miRs) have been implicated in the cell cycle and progression, cell migration, invasion, immune response evasion and apoptosis suppression for melanoma development and progression. Some down-regulated microRNAs involved in cell cycle and progression are miR-193b and miR-206 [8,9]. miR-211 and miR-30b/30d are involved in cell invasion while up-regulated miR-21 and down-regulated miR-205 are involved in apoptosis suppression for melanoma development [10] (Fig. 1). Histone modifications have also been implicated in melanoma pathogenesis. For instance, enhancer of zeste homolog 2 (EZH2) regulates gene expression by methylation of lysine 27 on histone H3 and its over-expression is associated with high proliferation rate and increased tumor thickness [10]. Numerous ongoing studies are focusing on the development of EZH2 inhibitors and some have even shown quite promising results against melanoma [10]. DNA methylation also correlates with melanoma development. Several genes such as GATA4, MGMT, RAR-b2 and RASSF1A exhibit hyper-methylated status in the melanoma progression. These highly methylated genes have been proposed to be used as diagnostic and prognostic biomarkers [10] (Fig. 2).

Skin cancer can be prevented by monitoring and eliminating the causative agents. It can be effectively controlled by blocking the blood supply to the tumor which limits the tumor growth and ultimately results in the enhanced survival of patients. Skin cancer can also be treated by radiation therapy, laser therapy, chemotherapy, cryotherapy or by surgical elimination. Among these, CO_2 laser therapy (use of heat) and cryotherapy (use of low temperature) have been used for tumor tissue ablation and can be applicable at any site to which melanoma has been metastasized, such as hepatic or cerebral tissues and lymph nodes [11].

In this review, we have discussed various treatment strategies for skin cancer, with special focus on the possible therapeutic options for melanomas. Anticancer phytochemicals which may be useful for the melanoma treatment have also been discussed.

2. Classical pharmacotherapy

Classical pharmacotherapy involves the introduction of topical drugs for the treatment of skin cancers. Some of the US Food and Drug Administration (FDA) approved topical drugs are described below:

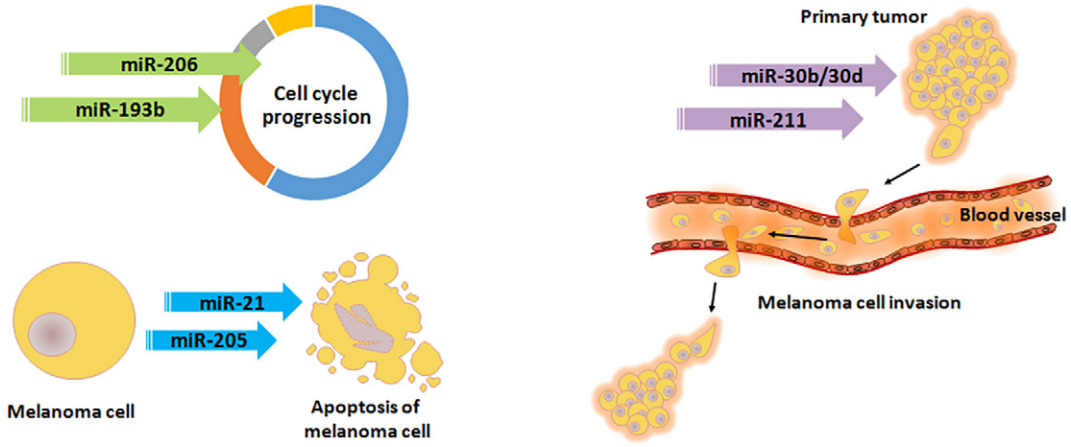

Fig. 1. Role of different microRNAs in cell cycle and progression, cell invasion and apoptosis in malignant melanoma.