Critical Reviews in Oncology/Hematology 115 (2017) 36–49

Contents lists available at ScienceDirect

Critical Reviews in Oncology/Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Review

Melanoma antigens and related immunological markers

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Contents

ARTICLE INFO

Article history:
Received 9 April 2017
Received in revised form 1 May 2017
Accepted 2 May 2017

ABSTRACT

Melanoma is a highly lethal cancer deriving from transformed dermal melanocytes. Early diagnosed primary melanoma may be curable, but the cure-rate of more advanced stages is limited, with high mortality rate. With the progression of the tumor, the melanocytes overexpress intracellular or

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http://dx.doi.org/10.1016/j.critrevonc.2017.05.001

Keywords:
Melanoma
Melanocyte
Melanoma antigen
Tumor-associated antigen
Melanoma marker
Anti-melanoma antibody
Melanoma diagnosis
Cancer immunotherapy

cell-surface molecules, including ectopic normal and tumor-specific proteins. Some of these induce a specific immune response by T and B lymphocytes. Antibodies raised against melanoma antigens were proposed for differential disease diagnosis, staging, prognosis and evaluation of treatment efficiency. Nevertheless, treatments based on stimulation of specific anti-melanoma immune responses have had only limited success. It seems that efficient immunotherapy should become more feasible pending on finding new adequate antigens to target. New insights into immune regulation of the tumor microenvironment and its progression may help the development of more successful treatments. We present here up-to-date information on known major melanoma-associated antigens, which could serve as tools for diagnosis as well as for clinical immunotherapy. This approach with promising results for treating some other selected malignancies is still experimental with a very limited success in melanoma. The development of new immune modulators of the tumor microenvironment and neo-antigens may be additional promising directions and may open new opportunities for the immunotherapy of melanoma.

1. Introduction

1.1. Malignant melanoma

Malignant skin cancers include basal cell carcinoma (basalioma), squamous cell carcinoma and melanoma. Though malignant melanoma (MM) accounts for only 5% of skin cancers, it is responsible for 90% of skin cancer-related deaths, while the incidence of disease is on the rise with an estimated 133,000 new cases reported worldwide annually (Erdmann et al., 2013; Gordon, 2013; Jennings and Murphy, 2009; Lens and Dawes, 2004; Sitas et al., 2013; Volkovova et al., 2012; Geller and Annas, 2003; Marks, 2000).

MM is derived from transformed melanocytes. The melanocytes contain high concentration of melanin, the predominant pigment associated with tissue discoloration of the skin, hair, eyes and certain areas in the nervous system (Freudenstein et al., 2004; Brat et al., 1999; Liubinas et al., 2010; Louis et al., 2007; Markert and Silvers, 1956). The skin melanocytes reside within the basal layer of the epidermis and in the hair follicles and they block overexposure to light while reducing the penetration of damaging ultraviolet radiation, but they may be present also in other ectodermal tissues, such as the brain and eyes. The melanocytes homeostasis is regulated by cells of neighboring tissues, such as epidermal keratinocytes, which stimulate skin melanocytes to produce melanin (Markert and Silvers, 1956; Valyi-Nagy et al., 1993; Quevedo and Fleischmann, 1980; Hearing, 2005; Goding, 2007).

A series of mutations in the regulatory genes of the melanocytes, which control cell proliferation and the production of growth factors may result in melanoma transformation (Hodis et al., 2012). Mutations in the regulatory genes of the transformed melanocytes' changes their phenotype, cause loosening of their adhesion receptors, while intracellular signaling is disrupted, and cell growth regulation by epidermal keratinocytes is compromised. These changes may result in the induction of the proliferation of the transformed melanocytes and their spread in nevi or moles which may develop to MM (Clark et al., 1984; Meier et al., 1998; Hsu et al., 2002). Melanoma progression is divided into five stages (Balch et al., 2009). Some of these stages, which can be identified by immunological markers, are characterized by the appearance of typical antigens (Brasseur et al., 1995; Hodi, 2006; Barrow et al., 2006). Fig. 1 summarizes the different developmental stages of MM. At stage 0 (termed *in-situ* melanoma), the melanoma is located as a nevus, which is restricted to the epidermis layer with minimal interaction with the blood vessels which are not present in this skin layer. Most skin nevi are benign with no involvement of transformed cells. However, transformed melanocytes can progress to stage I, the radial-growth phase (RGP), causing intra-epidermal lesions and local minor tumor cell invasion, termed the transformed phase of melanoma. The severity of the next stages is determined by tumor thickness and ulceration status. When the tumor progresses to stage II it gets to a vertical-growth phase (VGP) with invasion into the vascularized dermis, which is associated with increased risk of developing metastatic disease. RGP or VGP can develop directly from melanocytes or nevi, and progress directly to metastatic MM. At these stages, the primary melanoma can still be removed by radical surgical excision, with a high rate of complete local control and prevention of the spread of metastatic disease. Following progression into stage III, melanoma cells spread to the regional lymph nodes to form local metastases, and at stage IV, distantly spreading metastases are detected (Clark et al., 1984).

Melanoma is often not detected at stages I–III and the first clinical signs of the disease are diagnosed only at the stage of metastatic spread (Jennings and Murphy, 2009; Balch et al., 2009; Ozgen, 2014). This is in part due to the fast migration capability of the melanoma cells and their mobilization via an intra-vascular pathway by invading the blood and lymph circulation. Recently an extravascular migratory pathway was proposed along the pericytes on the external vascular surface in the remote target organs in a process called extravascular migratory metastasis (Landsberg et al., 2016; Zadran et al., 2013; Lugassy et al., 2013a,b; Lugassy and Barnhill, 2007). It is of interest that in many cases, metastatic spread may occur even before the primary tumor mass has been detected or following the spontaneous disappearance of the primary tumor (Damsky et al., 2014; Bedrosian et al., 2000). The patterns of metastatic spread are highly varied and unpredictable. The skin, lungs, liver, brain, and spinal cord are particularly common sites for metastatic dissemination, but other organs may be involved (Damsky et al., 2014; McDermott et al., 1996; Tas, 2012). Distant metastases are rarely resolved by surgical intervention and the response of local, as well as metastatic melanoma to radiotherapy or chemotherapy has so far been only marginal to modest (Garbe et al., 2011; Boyle, 2011; Fonkem et al., 2012).

MM cells express specific antigens that can be used as targets for immunotherapy by the induction immunological antitumor responses. This led to the spontaneous regression of pre-diagnosed melanoma in the early stages, a phenomenon whose rate of occurrence is hard to quantify. Such immune activating antigens could be used as a basis for a successful anti-tumor immunotherapy (Hodi, 2006). However, the treatment of most aggressive solid tumor malignancies, including melanoma, failed to yield significant long-term cure rates. Therefore, the development of new approaches, with treatments that could overcome high in-tumor phenotypic variability, still remains a major challenge.

1.2. Approaches for antibody and cell-based immunotherapy for melanoma

Identification and characterization of melanoma-associated antigens (MAA) may contribute to a better understanding tumor development, progression, differentiation and metastatic dissemi-