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REVIEW

Unveiling Similarities and Differences Between Cutaneous and Ocular Melanomas

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Abstract

Melanomas are outstandingly aggressive cancers, still their incidence is increasing. They can occur in the skin as cutaneous melanoma or in the eye as ocular melanoma. Their pathogenesis is generally similar; however, the prognosis of ocular melanoma patients is still poor, due to its special genetic profile and tumor microenvironment.

Here we review the similarities and differences between cutaneous and ocular melanoma, with a focus on their prognostic significance, their molecular signature, and their tumor microenvironment, in order to understand the strategies adopted to escape immune response.

Gathering and understanding available knowledge of melanomas and their specificities may help to identify the group of patients with the unfavorable prognosis in order to identify more effective treatments.

Keywords: Cutaneous melanoma, Uveal melanoma, Conjunctival melanoma, Tumor microenvironment, Immunotherapy

1. Introduction

Melanomas are a potentially devastating malignancy; they are principally divided into cutaneous melanoma (CM) and ocular melanomas. The last may affect either the uvea or the conjunctiva as uveal melanoma (UM) or conjunctival melanoma (CoM) respectively [1]. CM is the 19th most common cancer worldwide [2]. It is the deadliest and the most agressive form of skin cancer [3]. Its incidence is increasing especially among white population [4].

UM is the most frequent cancer in the adult eye, with a low incidence rate in Africa and Asia (0.2−0.3 cases per million per year) [5]. Once metastasis occur, the prognosis remains very poor [6]. The majority of ocular melanomas develop in the uveal tract, although the remaining cases mostly come from non-uveal areas like the conjunctiva [7]. CoM is the uncommon malignancy with an increasing incidence among Caucasian population [8,9]. According to epidemiological studies, conjunctival and CM are generally similar [10]. About 53−75% of instances of conjunctival melanoma are thought to result from primary acquired melanosis (PAM) with atypia; it can also grow from a conjunctival nevus or formed de Novo without any preceding lesion, and it occurs in 18−30% of tumor cases [11−13].

Over the last several years, a significant number of clinical trials have been carried out investigating novel approaches to activate and strengthen antitumor immunity. It has been shown that immunotherapy is beneficial against various types of cancer such as non-small cell lung cancer, renal cell carcinoma, and melanoma [14]; and has been suggested otherwise as a good and promising treatment option. However, patients with ocular melanomas including UM and CoM showed limited response rates; and still to date no standard treatment option for metastatic patients [15,16].

Therefore, understanding how these diseases work at the molecular level is an important part of coming up with novel effective ways to treat them.

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The present review shed light on the molecular similarities and differences between melanomas, to comprehend their microenvironment, their immune escape tactics, as well as their different treatment approaches in term of immunotherapy.

2. Pathogenesis and genetics

Melanomas are aggressive type of cancer [17]. They arise from an abnormal division of melanocytes which confer the color of the skin and the eyes [18].

CM is thought to be a multifactorial disease, which means that it is influenced by both genes and environmental risk factors. Ultraviolet radiations are the most important environmental risk factor for CM because they can cause both genotoxic and mitogenic effects when the melanocyte genome interacts [19].

UM and CoM are quite different diseases with separate origins and genetics [20]. The potential significance of ultraviolet radiation in the emergence of UM and CoM is still being debated [21−23]. Beyond, UM is an intraocular tumor that affects the iris, ciliary body, or choroid [24]. Whereas, CoM is a type of mucosal melanoma that begins in the conjunctiva and looks very similar to CM [25].

Although CM, UM, and CoM are similar in appearance under the microscope they develop in quite different ways. Briefly, UM tumors are unusually devoid of the oncogenic BRAF, NRAS, and TERT mutations that are seen in 15%−50% of CM and CoM [26,27]. On the other hand, UM has a defect in the GNAQ, GNA11, and BAP1 genes [28].

3. Prognosis

Clinical, histopathological, and cytogenetic markers can be used to predict the prognosis of melanomas. Several factors contribute to the poor prognosis of CM including site of the tumor, tumor thickness, ulceration, mitotic rate, high tumor vascularity, lymphovascular invasion, and genetic factors such as BRAF mutation status [29].

Regarding ocular melanomas, white population, tumor location, large tumor size, increasing tumor thickness and diameter, subretinal fluid, pigmented melanoma, as well as epithelioid cell type are the major prognostic factors [30]. Distinctively, UM has a specific propensity to migrate to the liver, with 80−90% of metastatic UM patients ultimately demonstrating hepatic involvement; making it one of the most aggressive type of melanomas with a worse prognosis [31]. To point out further, the prognosis is poorer for patients who have epithelioid cells. The highest basal diameter and thickness of the tumor serve also as crucial prognostic indicators. The TNM staging system divides UMs into prognostic categories based on the tumor's size, ciliary body involvement, and extrascleral expansion. In addition, chromosome 8q gain, chromosome 6p gain, and chromosome 3 deletion are examples of frequent chromosomal markers that affect the prognosis of UM [32,33].

4. Tumor microenvironment

The human immune system is critical for tumor growth and control, and tumor cells, for their part, may employ mechanisms to evade the immune response [34].

Regarding CM, it is reported to be highly immunogenic and marked by the infiltration of different immune cells in comparison with both UM and CoM due to its elevated mutational burden [35].

The microenvironment of CM and CoM is characterized by the presence of B cells, M1 and M2 macrophages, dendritic cells, neutrophils, CD4+ T cells, and CD8+ T cells, as well as high production of TGFB [36]. Distinguishably, in the UM microenvironment, abundant infiltration of NK cells, M2 macrophages especially TAMs, and T cells including CD8+, CD4+, Treg, and T helper are found. As well as high production of IL-6, IL-10, IFN, TGFB, and MHC class 1 that prevent NK cells and T cells function and also decreases anti-inflammatory cells in the eye microenvironment. In consequence, it confers an immunosuppressive microenvironment [37].

Notably, M2 macrophages were highly present in the various forms of melanomas and they were linked to an immunosuppressive profile as well as angiogenesis [38]. As a result, inflammation is regarded as one of the hallmarks of melanoma [39,40]. Thus, investigating the strategies used by UM cells to avoid immune response may lead to a better understanding of resistance to previous failed treatment strategies [41,42]. This special microenvironment confers a poor prognosis to UM patients, which enables it to escape the immune response via diverse processes including the production of indoleamine 2,3dioxygenase (IDO), expression of an altered Fas Ligand and overexpression of PDL-1 that were found to dampen the T-cell response [43]. The genetic traits of UM cells and their potential to adopt immunosuppressive tactics from the places where they arise assist in dodging the immune system and lead to checkpoint inhibitor resistance.

5. Treatment

CM care has taken a quantum leap forward. Anti-PD-1, anti-CTLA4, and anti-PD-L1 antibodies have been used extensively in the treatment of CM [44]. Survival rate for individuals with advanced melanoma was first demonstrated to improve with immune checkpoint treatments. To demonstrate, Ipilimumab is the first immune checkpoint inhibitor (anti-CTLA4) to be approved by the FDA for metastatic melanoma patients [45]. Nivolumab and Pembrolizumab also have exhibited positive outcomes in CM patients and some patients are now seeing long-term and stable tumor remission [46−50].

Given their molecular and pathophysiological similarities, response to immunotherapy of CM and CoM in metastatic patients is generally common. However, more formal trials are needed to confirm and find more effective treatments for CoM patients. Nevertheless, although current clinical data are rare, UM was reported as unresponsive to many conventional therapies, and the median overall survival for individuals with this illness remains restricted [51].

Most medications used to treat metastatic CM have been generally unsuccessful in the UM environment and no systemic treatment has shown improved clinical results in UM patients so far [52]. Targeted treatment studies for advanced UM have fallen short with other treatments, such as the MEK1/2 inhibitors Selumetinib and Trametinib [53]. Checkpoint inhibition using PD-1-blocking antibodies, such as Pembrolizumab, has also been explored in metastatic UM, with comparable outcomes (ranging from 3 to 11%), with a cutoff date of 29, 33, and 49 weeks since starting therapy respectively; as well as a median progression-free survival of 18 weeks [54]. In clinical studies, Ipilimumab and Tremelimumab have demonstrated modest clinical effectiveness for advanced UM patients; Ipilimumab's first cycle's median survival time is 10.3 months versus 12.8 months with Tremelimumab [55,56].

Notably, the poor response rates and insignificant impact on survival of monotherapy checkpoint inhibition in UM dramatically contrast with positive outcomes in CM. As a result, exploring alternative immunological checkpoint pathways are needed in order to find the optimal treatment strategy for those patients.

6. Conclusion

Cutaneous, uveal and conjunctival melanomas derive all from melanocytes; thus, they share the same origin and cellular role. Nevertheless, they differ in genetic and immunologic aspects, leading to different treatment response profiles among patients. Accordingly, the fact that immune checkpoint inhibitors only help certain melanoma patients highlights the need to scrutinize in its immune microenvironment and to identify predictive indicators to overcome escaping immune surveillance and developing resistance. Therefore, it is crucial to learn more about the immunosuppressive processes that keep UM patients from getting better therapy and to find more immunologic pathways that may be implicated in this form of cancer.

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Conflicts of interest

The authors declare no competing interests in this case.

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