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Uveal *vs.* cutaneous melanoma. Origins and causes of the differences

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Abstract Melanoma is a malignant tumour derived from melanocytes (dendritic cells originated from the neural crest and capable to produce melanin synthesis) that could be established on the skin or less frequently on the uvea. The cellular origin from both kind of melanoma seems to be the same but the melanocytes migrates to the epithelia for cutaneous melanoma, while for uveal melanoma, they migrate to mesodermic tissues. Despite the common origin, both melanomas show extreme differences in their metastatic potential, clinical response to treatments, immune response and genetic alterations. We will describe some of those differences in this review.

Keywords Melanoma · Stem cells · Uvea · Skin

Introduction

Melanoma is one of the tumours that has shown the highest rate of increase in the last decade in western countries [1]. The highest rates worldwide are amongst fair skinned populations from Australia and New Zealand, where they have reached epidemic proportions (males: 50 cases/100,000 habitants/year; females: 37/100,000) [2].

Melanomas of the ocular and adnexal structures comprise around 5% of all melanomas, and 85% are of uveal origin [3]. Uveal melanoma is the most frequent primary malignant intraocular tumour in adults. The tumour arises from melanocytes located in the iris, the choroid and the ciliary body, which are the structures of the uveal tract. The reported incidence from several countries ranges from 4.9 to 10.9 per million population, remaining stable for the last 50 years. Uveal melanoma is most commonly seen in an older age group of white population with light skin, hair and eyes, with a progressively rising age-specific incidence rate that peaks at the age of 70 years [4, 5].

It usually presents as a pigmented choroidal nodular mass in the eye fundus, in the early stages, growing towards the vitreous space, with a mushroom or multilobular shape and associated retinal detachment in advanced stages; and growing at the end towards the extraocular structures through the emissary channels or the optic nerve. Accuracy in diagnosing choroidal melanoma with indirect ophthalmoscopy and ultrasound by expert ocular oncolo-

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gists has improved in last 30 years from 80% [6] to more than 99.5% [7].

Objectives for treatment include tumour destruction, preservation of the eye and visual function, and improvement of survival. Treatment options range from observation (small, inactive tumours) to enucleation (large tumours without potential for visual recovery), but the most extensive conservative therapy is episcleral brachytherapy or charged-particle radiotherapy. This technique has proven to result in excellent local control with a 5-year recurrence rate of less than 5%, and survival rates similar to those of enucleation [8, 9].

Although significant advances have been made in the ability to diagnose and treat primary uveal melanomas, they have unfortunately not been accompanied by improvements in the survival rate of the patients. Mortality rates have not changed in the last few decades and reach more than 40% of patients developing systemic disease and dying within 10 years of diagnosis [10]. This fact suggests that the disease was already disseminated at the time of diagnosis [11] either as circulating malignant cells (CMCs) [12] or as occult micrometastatic lesions [13]. Unfortunately, current clinical tests fail in detecting metastatic disease at an early stage [14]. Once the disease has metastasised, life expectancy is reduced to <1 year [15]. Treatment options for patients with clinically disseminated disease are scarce and usually unsuccessful.

The treatment of intraocular melanoma has recently evolved. Enucleation has been superseded largely by brachytherapy, proton beam radiotherapy, stereotactic irradiation, transcleral local resection, transretinal resection and diode laser phototherapy [16]. The principal diagnostic parameters are tumour diameter, age and sex of the patient, together with the histology and localisation of the tumour [17].

Causes of the diversity of the melanomas

The Caucasian race seems to be the most significantly affected, with light skin colour, blond hair and blue eyes being specific risk factors to oncogenic effects of sunlight.

Ultraviolet light has been involved in the genesis of several cutaneous melanomas [18]. It has been suggested that melanomas were due to an intense and intermittent exposure to sunlight, that do not leave time for melanocytes to synthesise melanin to protect them from ultraviolet irradiation (UV), producing DNA mutations. Although there is evidence that supports this hypothesis in skin melanoma, the evidence regarding uveal melanoma is insufficient and contradictory [19].

Although they are both of neural crest origin, significant differences can be found between cutaneous and choroidal melanocytes and cutaneous melanoma derives from melanocytes that migrates to the epithelia [20] while uveal melanoma derives from melanocytes that migrate deeply to mesodermic tissues [21]. A better molecular understanding of these cellular populations could help to understand the variability of the behaviour and response to therapies of both melanomas [22].

In this context, cell cycle associated proteins have been singled out as the main cause but other parameters such as stem cell origin, immunological diffferences, etc, also have been suggested [23]. We will discuss some of these hypotheses in this review.

Melanoma stem cells

The cancer stem cell (CSC) hypothesis opened new perspectives for the treatment of tumours. CSCs have been identified in several malignancies by type-specific cell surface markers often associated with stem cells [24–27].

There are two proposed genetic origins for cancer [27] (Fig. 1). The stochastic model predicts that every cell within a tumour can form new primary tumours, and this mechanism forms the basis of most tumour therapies. By contrast, the hierarchical or stem cell model predicts a rare subset of cells as tumorigenic. The tumour is heterogeneous in appearance, consisting of cells at different degrees of differentiation. The discovery that bone marrow-derived stem cells home to sites of tissue damage [28, 29] opens up a third possibility for the origins of cancer. Normal stem cells could migrate to the tumour and fuse with mutated somatic cells, giving rise to immortal, malignant CSCs [30]. This hypothesis can explain both the heterogeneity of this kind of tumour and their variable responses to several conventional therapies (Fig. 2).

Melanocytic stem cell migration to different areas

Melanomas are believed to arise from a mature, differentiated melanocyte. With regard to cutaneous malignancies, increasing evidence supports the stem cell theory in the pathogenesis of squamous cell carcinoma and malignant melanoma. In this scenario, a transformed, differentiated melanocyte may have undergone dedifferentiation and regained stem cell properties such as self-renewal [31]. Melanocytes found in the skin and in the choroid layer of the eye derive from the neural crest, a transitory structure formed at the dorsal borders of the neural plate during development of vertebrates. Melanocytic precursors, melanoblasts (which themselves are unpigmented but have the potential to produce melanin) invade all skin areas and differentiate into melanocytes. How neural crest cells become committed to the melanocytic lineage for eye or skin and which factors control survival, proliferation and differentiation of melanocyte precursors are still not completely clear.

The analysis of mouse white spotting mutants allowed the identification of stem cell factor (SCF, also denominated as steel factor) and its tyrosine kinase receptor c-Kit as crucial components of a pathway required for survival and migration of pigment precursors cells [32]. Other studies characterised the implication of endothelins [33], in particular endothelin-3, to be required together with SCF/c-Kit for migration of early melanoblasts in the dermis [34]. An-

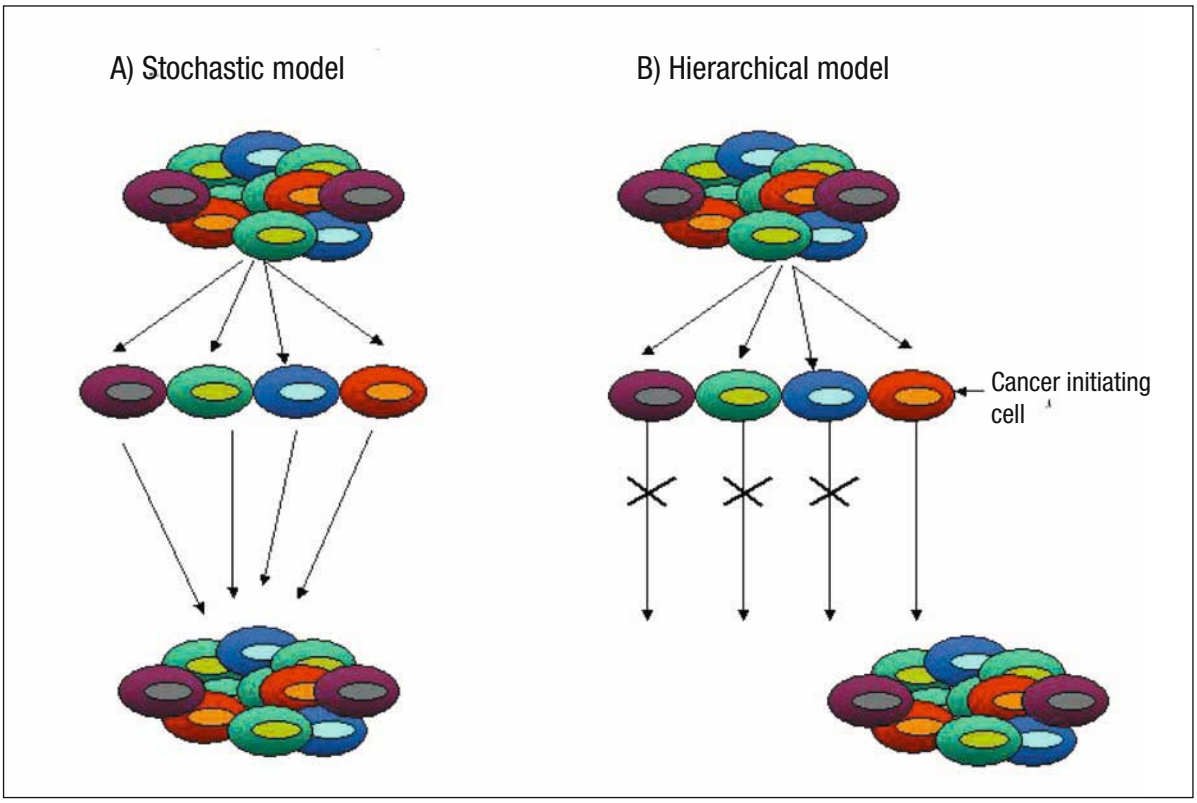

Fig. 1 Stochastic vs. hierarchical model of tumour formation. In the stochastic model of carcinogenesis, cells form a heterogeneous tumour from which each cell is able to randomly give rise to new carcinomas. In the hierarchical model of carcinogenesis, just a few cells (<5% of tumour mass), known as the CSC, are able to originate new tumours

other pathway likely to be involved in melanocytic migration is Wnt/beta-catenin, which controls neural crest cell fate and also activates Mitf expression [35, 36]. In fact, Fang and colleagues [37], using a combination of Wnt3a, endothelin-3 and SCF, were able to derive melanocytes from human embryonic stem cells. These melanocytes were able to migrate to the epidermal basal layer in reconstituted skin.

Stem cell markers

Like the treatment of many types of cancer, that of cutaneous and uveal melanomas could benefit tremendously from the identification of specific tumour stem cell markers. But the scarcity of these cells within the tumour mass (that comprise >99.9% of most cancers) makes this a major technical challenge. In addition, many tumour stem cell markers are probably shared with normal stem cells. Tumour-specific patterns of gene expression, designed to allow the tumour stem cell to survive outside its protective "niche" in normal tissues, will be the best initial targets for new therapeutic agents.

These and other studies demonstrated that aggressive melanoma cells share many characteristics with embryonic progenitors. Stem cells have a complex relationship with their microenvironment, which exerts a crucial role in all stages of tumorigenesis including initiation, progression and metastasis [38]. Lastly, a number of laboratories have shown that an embryonic microenvironment has the capacity to reverse the metastatic phenotype of cancer cells. Thus, several studies have documented that embryonic microenvironments reprogramme aggressive melanoma cells towards a less aggressive phenotype [39]. Furthermore, these studies have uncovered Nodal, an embryonic morphogen belonging to the TGF-β family, as an important factor for sustaining melanoma aggressiveness and plasticity [40].

Attempts to isolate cancer stem cells in malignant melanoma

A population that fulfils the criteria for melanocyte stem cells was identified by Nishimura and co-workers in the lower permanent portion of mouse hair follicles [41]. However, it is unknown whether this cell population is multipotent or restricted to the melanocytic lineage. Interestingly, a population of multipotent adult stem cells, which gives rise to differentiated smooth muscle cells, neurons and melanocytes, has been isolated from human hair follicles [42].

CSCs from brain tumours could be isolated, and proliferate as nonadherent cell aggregates termed "spheres or spheroids" [43]. It has been speculated that the association between tumours of the nervous system and malignant melanomas in certain individuals represents an underlying abnormality in neural crest stem cells. In 20% of the

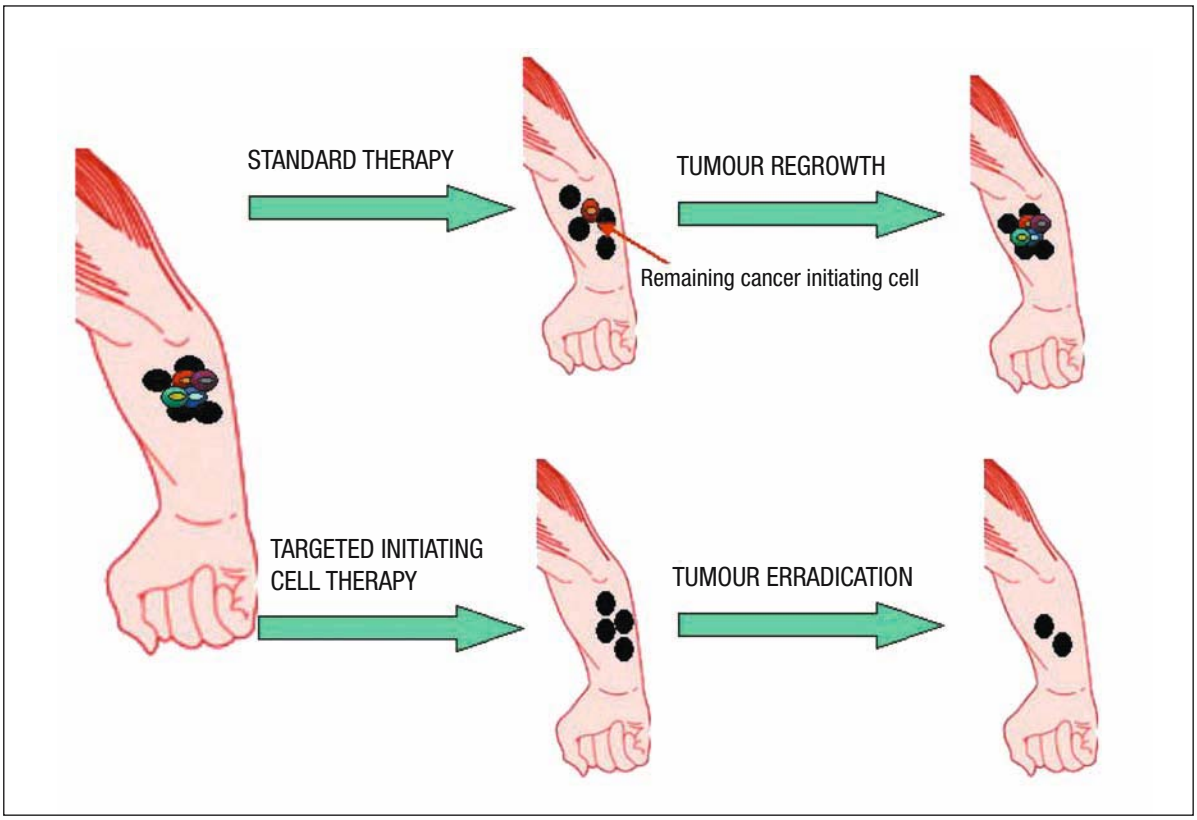

Fig. 2 CSC-targeted therapies: CSCs are often the population which shows resistance to chemotherapy. The lack of effectivity against these cells is sufficient to allow regrowth of the tumour. In the new CSC-targeted treatment model, elimination of these CSCs may prevent tumour recurrence

metastatic melanomas cultured in growth medium suitable for human embryonic stem cells, a subpopulation of cells propagating as nonadherent spheres was found, whereas in standard medium, adherent monolayer cultures were established. Individual cells from melanoma spheres (melanoma spheroid cells) could differentiate under appropriate conditions into multiple lineages, such as melanocytic, adipocytic, osteocytic and chondrocytic lineages, which recapitulates the plasticity of neural crest stem cells [44].

Recently, in other studies, the ability to efflux Hoest dye was utilised in another attempt to isolate cells with stem cell-like features [45]. These cells also expressed the stem cell-associated surface marker CD133 (as the CSCs in brain tumours) and the chemoresistance mediator ABCB51. In serial human-to-mouse xenotransplantation experiments, ABCB51 melanoma cells possess greater tumorigenic capacity than other populations and re-establish clinical tumour heterogeneity. *In vivo* genetic lineage tracking demonstrates a specific capacity of ABCB51 subpopulations for self-renewal and differentiation. Identification of melanoma-initiating cells with enhanced abundance in more advanced disease but susceptibility to specific targeting through a defining chemoresistance determinant has important implications for cancer therapy. All these data should be tested to determine whether or not they are applicable to uveal melanoma.

Genetics in uveal melanoma

New prognostic factors in uveal melanoma have been described and they could also serve as molecular targets for the development of novel therapies. These prognostic factors/molecular targets, include membrane receptors, enzymes, cytokines, cytoskeleton components, oncogenes, tumour suppressor genes, cell-cycle proteins and nuclear antigens. The recent development of DNA micro-array technology offers an unprecedented possibility to study these molecules and others associated to malignant transformation.

Data from several transcriptome analysis [46] suggest that at least three main molecular pathways have frequently been found to be dysregulated in melanoma tissues. These pathways include the Ras-Raf-MEK-ERK pathway detected as constitutively activated in skin melanoma due to frequent mutations in BRAF (60% of cases) and NRAS genes (20% of cases) [47, 48]. Functionally, oncogenic RAS maintains cells in a proliferative status and contributes to the activation of the PI3K-AKT pathway [49]. Constitutive activation of this second main dysregulated pathway in melanoma is reinforced by the frequent chromosome deletion of locus 10q harbouring the PTEN gene found in this cancer type [50, 51]. This pathway controls cell cycle progression [52], provides strong survival signal [49] and regu-

lates crucial cellular functions including adhesion, angiogenesis, and resistance to drug treatment [53]. Experimentally it has been suggested that aberrant activation of these two pathways in melanoma cells may be necessary but not sufficient to promote melanoma progression. Therefore observation that the $p16^{INK4A}$-CDK4-RB tumour suppressor pathway is also frequently inactivated in skin melanoma at intermediate stage [54] suggests that these three pathways may band together to provide the crucial biological functions required for the metastasis process.

In contrast to the well described genetic alterations found in cutaneous melanoma, not much is known about genes associated with the development of uveal melanoma, mainly because of the small number of biopsy samples accessible from patients developing this disease. However it has been demonstrated [55, 56] that uveal melanomas develop characteristic chromosomal abnormalities, such as loss of chromosome 3, abnormalities in chromosome 6 and, less frequently, gains in chromosome 8q. This is associated with a reduction in the 5-year survival from approximately 95% to less than 50% [56].

Uveal melanoma and immune response

Melanomas of the eye have the advantage of growing in the special environment of an immune privileged site and it has long been shown that the special immunosuppressive properties of the intraocular microenvironment are essentially mediated by cytokines.

The immune surveillance hypothesis was introduced over 30 years ago [57] and it proposes that neoplasms express novel antigens that subject them to immune detection and elimination. In order for immune surveillance to be effective in controlling neoplasms, the tumour must arise in a body site that permits induction of the full array of immune responses. The unique immunologic and anatomic features of the eye prevent the induction and expression of conventional immunity – a phenomenon known as 'immune privilege'. However, ocular immune privilege represents a theoretical obstacle to immune surveillance. The presence of either tumour-infiltrating lymphocytes (TIL) or tumour-infiltrating macrophages (TIM) is associated with poor prognosis in uveal melanoma patients [58] and suggests that some immune responses to intraocular tumours might exacerbate, rather than mitigate, tumour progression.

Clinical response in uveal melanoma

Certain natural properties of melanoma stem cells are likely to increase the tumour resistance to standard chemotherapy agents. As CSCs are believed to be more resistant to our current chemotherapeutics, allowing them to persist and regenerate tumours, understanding these different expression patterns will be of paramount importance in producing more effective treatments. Therefore, in developing new cancer therapeutics, the toxicity towards tumour stem cells is an important priority [59]. Thus, if cancer therapies do not effectively target the CSC population during initial treatment, relapse may occur.

Uveal melanoma is characterised by constitutive chemoresistance. The chemoresistance of uveal melanoma is mainly due to the typical multidrug resistance phenotype (MDR), which is linked to overexpression of membrane proteins that actively extrude anticancer drugs from the cell. Typical MDR is particularly complex in this tumour as several chemoresistance-related proteins are simultaneously produced [60]. The negative prognostic significance of the overexpression of P-glycoprotein, the main representative among the typical MDR-related proteins, was shown in uveal melanoma. The atypical MDR phenotype, which refers to other chemoresistance mechanisms such as resistance to apoptosis, also contributes to the chemoresistance of uveal melanoma.

Conclusions

Even with advances in the diagnosis and local treatment of uveal melanoma, there has been no significant change in the survival rates of these patients in the last decades. Metastatic disease still occurs at the same frequency, and no systemic therapy is currently offered to patients after local eye treatment. As a result of these limitations, there is interest in gaining a greater understanding of molecular changes associated with aggressive disease patterns in uveal melanoma. This might result in new, more effective and less toxic therapies as well as provide prognostic information for defining subgroups of patients with a less favourable prognosis as potential candidates for adjuvant therapies.

Therefore, as a stem cell population has been isolated in cutaneous melanoma, there is hope to isolate one in uveal melanoma. This may provide new targets for treatments.

Thanks to the recent progress in molecular biology, chemosensitisation strategies of gene therapy approaches, which aim at weakening the pathological activity of MDR genes in cancer cells, are currently on the rise. From the complexity of signalling involved in carcinogenesis, it is clear that each cancer is unique in the set of signals and group of cells involved in its development. Therefore, to develop newer, more effective treatments for cancer, several obstacles must first be overcome and further studies need to be done.

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