

## ORIGINAL PAPER

# Choroidal melanocytes and associated pathology

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### Abstract

The embryologic origins of choroidal and cutaneous melanocytes, also of the genes involved in cutaneous and choroidal melanoma, are identical, even the two kinds of tumors are different entities. This is a general scientific report, which stretches the molecular mechanisms, as basement of choroidal melanocytes proliferation.

**Keywords:** choroidal melanocytes, associated pathology.

### ☞ Introduction

The cell that has the ability to synthesis melanin is recognized as melanocyte. Its origin is represented by melanoblast cell. Were described both peripheral and central melanocytes. The peripheral melanocytes come from neural crest, and could be found further in epidermal layer, pillous hair bulb, meninges, internal ear and eyes; the central melanocytes are also recognized as pigmentary epithelial retinal cells [1].

Uveal melanocytes are located in iris stroma and cilliary body; choroida represents 80% of uveal tissue.

The melanocytes located in choroidal stroma and suprachoroidal, are fusiform/elongated, starry, round, ovalar, pigmented cells, with a central nucleus.

The choroidal melanocytes function is not well known. Probably the cytoplasmic fibrillary structures play a role in capillary tonus maintenance; there is no functional contact between choroidal melanocytes and other kinds of choroidal cells.

It seems that UV rays have an impact in uveal melanogenesis [2].

### ☞ Melanocytes' embryology and melanogenesis

The uveal melanocytes get birth in neural crest, which is a transitory embryologic structure.

The neural crests have origin in dorsal part of neural tube and represent the origin of all pigmented cells, excepting the epithelial retinal cells, which come directly from neuroectodermal structure.

It has been proved that melanoplasts migration takes place with dorsal-lateral trajectory between the dermomyothom and ectoderm. Few days later the migration period, the melanocytes reach an intensive

proliferation phase, in order to be differentiated in dendritic and pigmented cells.

In humans, the melanoblasts are colonized between 8<sup>th</sup> and 14<sup>th</sup> week of intrauterine life [3].

Melanogenesis (melanin-synthesis and its control mechanisms) takes place in two different types of cells: melanocytes and retinal pigmented epithelial cells.

In humans, the uveal melanogenesis appears in the 20<sup>th</sup> week of embrionary life and finishes in few weeks after delivery [1].

Uveal melanocytes can still produce melanin, few weeks, even after birth. In this way can be explained the fact that the color of the iris becomes permanent, after six moths of age.

The melanin is produced by the melanosome, a cellular organelle. The melanogenesis rules under the influence of numerous enzymes which catalyze progressively the reactions. The melanin precursor synthesis is an aromatic aminoacid:  $\alpha$ -tyrosine.

### ☞ Congenital pigmentation anomalies

#### Albinism

The albinism is characterized by melanin absence, in presence of a normal number of melanocytes. The absence or melanin synthesis decrease is associated at ocular level, with faveolar hypoplasia and optic fiber repartisation disturbance.

In humans were identified seven responsible genes of different types of albinism. The melanogenesis anomaly is responsible of *ocular-cutaneous albinism* (type I, II and III), and *X-linked ocular albinism*.

The melanosoms development and movement anomalies are responsible of: Griscelli and Hermansky–Pudlak syndromes (SHP), and Mediak–Higashi (SGH) syndrome.

## **Congenital ocular melanogenesis**

In physiologic conditions, there are pigmentary patches around the ciliary vessels orifices, which cross the sclera, or can exist a sclera congenital pigmentation; this pigmentation causes the *benign ocular congenital melanogenesis Bourquin (melanosis oluci or melanosis bulbs)* [4].

In congenital ocular melanogenesis, sclera and episclera have a bluish or dark greenish color. If the eyelids are also pigmented, covering the corresponding area of the trigeminal nerve's two branches is about ophthalmic-maxillary nevus.

### **☐ Ocular pathology linked with choroidian melanocytes proliferation**

#### **Choroidal nevus**

The choroidal nevus is a benign tumor that could be found in 6.5% in normal eyes [5].

The term *nevus* is defined as a focal colonization of melanocytes. The degeneration's risk of a choroidal nevus, is about 1/5000 [6, 7].

It is known that choroidal nevi may increase in size, but this evolution is seldom progressive [8].

The benign choroidal nevi develop a small size (1–5 mm in diameter) are flatted or mild prominent, asymptomatic. Is a real problem when these nevi are considered to be suspect; this situation might be met when sight disturbances appear, with retinal serous discoloration, or their sizes become larger (up to 7 mm).

When the increase in size of suspected nevi is documented, they are considered to be melanoma [9].

The melanocytoma is a melanocytic tumor of optic nerve papilla, histological being considered to be a nevus. Usual, melanocytes have smaller sizes than papilla, with a positive prognosis.

Zimmermann LE and McLean IW [10] appreciate that the melanocytoma derives from normal uveal melanocytes, similar to those form ocular melanoma. The papillary location is explained through abnormal persistence of uveal melanocytes in choroidal level of cribrated lama.

Malignant degeneration is exceptional rare [11].

#### **Choroidal melanoma**

The choroidal melanoma is a primitive malignant tumor, which incidence is estimated to be 0.7/100.000 inhabitants. The isolated cases of familial choroidal melanomas, sustain the existence of a predisposal genetic factor. There is a frequent association of uveal melanoma with type I neurofibromatosis, this neurofibromatosis not being considered to be a risk factor in melanoma occurrence [12].

The natural evolution of choroidal melanoma is variable. The little information regarding the evolution comes from patients, which refuse the enucleating procedure. Thus, is admitted that the choroidal melanoma increases slowly [13].

The vital prognosis depends on cells' type: elongated, epithelial or mix. These three cytological types are dictated by the cellular differentiation.

In a quite short period of time [14] was proved that in the same tumor the cytological phenotype can be changed. From cytological point of view, there were described three types:

- melanoma with type A fusiform cells (Figure 1);
- melanoma with type B fusiform cells (Figure 1);
- melanoma with epitheloid cells (Figures 2 and 3);
- the melanoma with type A fusiform cells, possesses an apparent microscopic benign aspect, with small elongated cells, elongated nuclei, with no apparent nucleoli, with no mitosis;
- the melanoma with type B fusiform cells possesses a pleomorphic respect; type A cells are mixed with epitheloid cells, with large ovalar nuclei, with mitotic activity.

The two different cell types may co-exist in the same tumor; there are tumors where the fusiform elongated cells possess a fascicled disposition. The epitheloid melanoma is composed by unequal cells, with rich cytoplasm; some cells are multinucleated bizarre nuclei (Figures 1 and 3).

The prognosis becomes unfavorable, in proportion with mitosis number.

### **☐ The implication of cellular and molecular factors in melanocytes proliferation and transformation**

In order to describe the cellular and molecular proliferation mechanisms, is used the term „message transmission” which starts with an extra cellular message, caught by a membrane receptor. The activated receptor sends the extra cellular message, inside the cell, special toward nucleus, inducing the transcription factor activation, who regulates the genes expression, among them, some are necessary the cell to enter in mitosis phase. In choroidal melanoma exists a hypothesis which sustains the existence of a disturbed regulation of intracellular signaling molecules, also of molecules involved in cellular proliferation and cellular cycle.

Among these could be found intracellular transcription proteins MEK/ERK, which control the expression of positive and negative regulators upon cellular cycle, also of prescription factors.

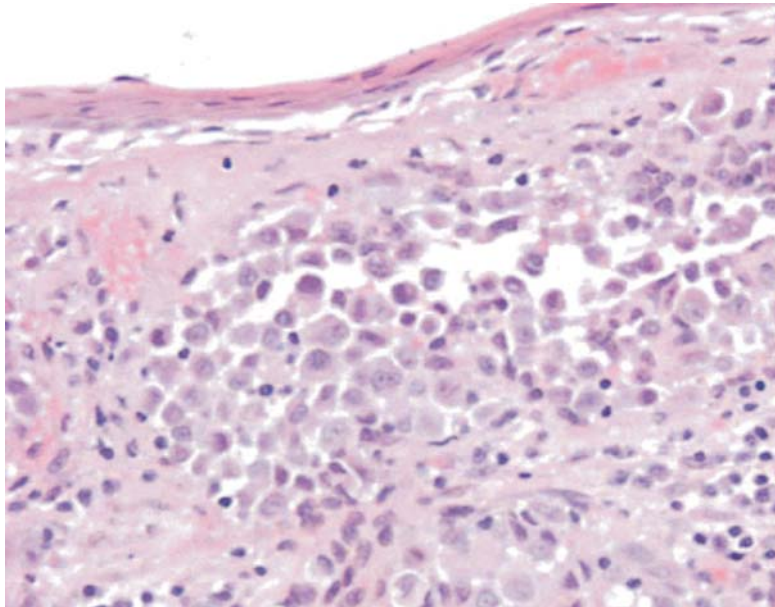
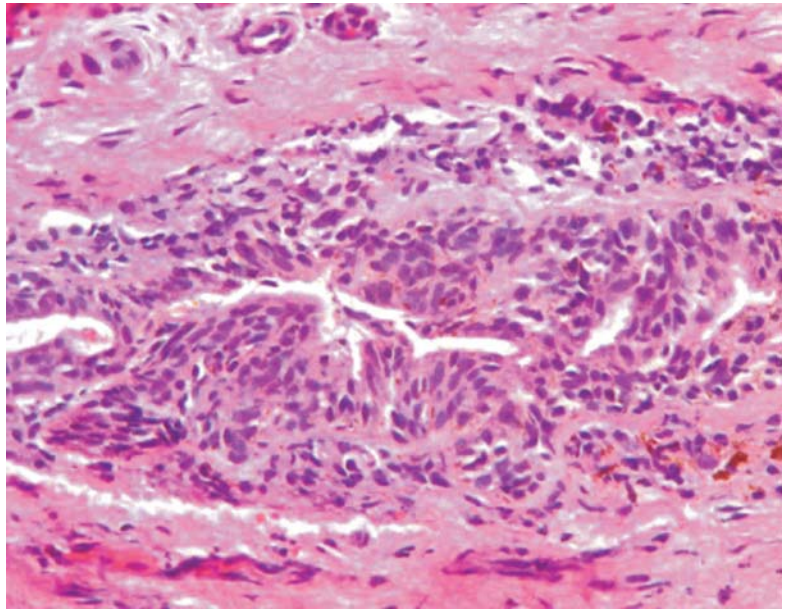
The hypothetic role possessed by MEK/ERK in choroidal melanoma genesis is confirmed by Weber's studies [15]. The growth factors study was proved that Insulin Growth Factor (IGF) can participate to hepatic metastasis in choroidal melanoma [16].

During last years, were studies targeted on c-kit receptor role, which its growth factor is represented by Stem Cell Factor (SCF); it participates in choroidal melanocytes stimulation [17].

### **☐ Conclusions**

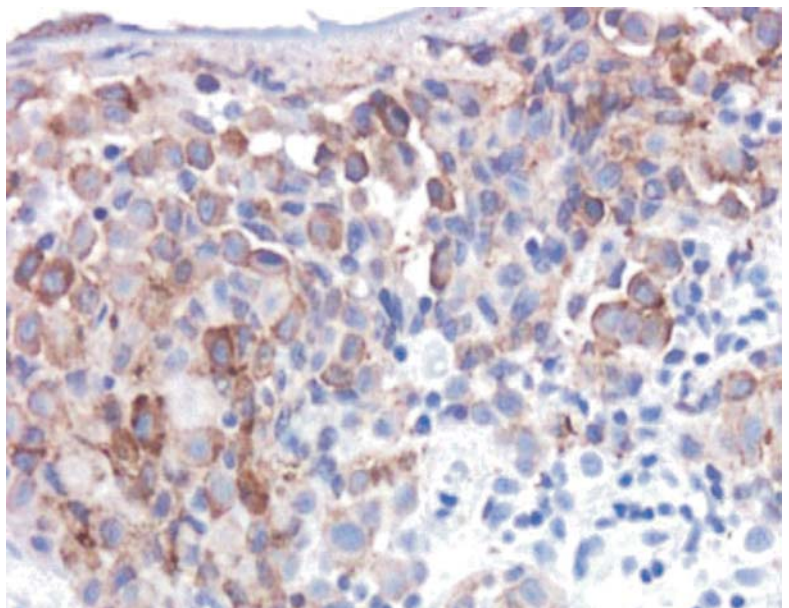
A better knowledge about cellular proliferation regulation mechanisms permits a higher understanding of carcinogenesis process. Plurifactorial molecular and cellular analysis takes into account cellular proliferation, apoptosis and cellular differentiation, in order to guide the researches into choroidal melanoma and its metastasis mechanisms.

**Figure 1 – Conjunctival melanoma with fusiform cells (HE, ×200)**



**Figure 2 – Choroidal melanoma with epithelioid cells (HE, ×400)**

**Figure 3 – Conjunctival melanoma with epithelioid cells and rich melanin pigment (HE, ×400)**



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