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REVIEW ARTICLE

Chromosomal instability landscape in uveal melanoma

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Summary

Uveal melanoma (UM) is the most common primary ocular malignancy demonstrating increased rates, especially in middle-aged Caucasian populations. Chronic exposure to ultraviolet rays/sunlight, race, gender (males), or some familial hereditary syndrome in sub-groups of patients are major factors correlated to increased risk for UM rise and progression. Specific genetic signatures at the level of chromosomal instability (CI) characterize sub-groups of patients affecting the biological behaviour of the tumour leading to aggressive phenotypes (advanced stage-distant metastases, poor response, and survival rates), especially combined chromosome 8 polysomy and chromosome 3 monosomy. Besides these aberrations, numerical and structural imbalances have been reported in chromosomes 1, 6, 8, 9, 11, 18, and 21. In the current molecular review we present specific chromosome numerical and structural aberrations that are implicated in UM genetic substrate and create a variety of genetic signatures in the corresponding patients.

Key words: *ocular, uveal, melanoma, genetics, chromosome*

Introduction

Concerning primary ocular malignancies in adults, uveal melanoma (UM) is the most common - although generally rare - among all malignancies-demonstrating increased rates, especially in middle-aged Caucasian populations [1,2]. The onset of UM implicates the eye uveal tract comprising iris, ciliary body, and retinal choroid. The corresponding target-cells are immigrated melanocytes from the neural crest to uveal tract [3]. The clinical image of the corresponding patients covers a broad spectrum from completely asymptomatic at the early stages of the lesion to painless modified or loss of vision (ie metamorphopsia). Flashing or light flickering under the term "photopsia" combined or not with discoloration of the iris and potentially chronic conjunctivitis have been reported. Different levels of asymmetric astigmatism as a result of intraocular lens displacement or in rare cases and blind eye are also clinical signs for development of an occult melanoma [4,5]. Chronic exposure to ultraviolet rays/sunlight, race, gender (males), or some familial hereditary syndrome in sub-groups of patients are major factors correlated to increased risk for UM rise and progression. Concerning familiar/genetic predisposing causes, ocular melanocytosis, dysplastic nevus syndrome, choroidal nevi, neurofibromatosis have been found to be critically involved in its development. Interestingly, conventional cutaneous melanoma seems not to be directly a risk factor for UM [6-8]. Specific UM genetic

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alterations explain in part an aggressive phenotype of the malignancy characterized by increased metastatic potential. UM demonstrates significant proportions hematogeneous and lymphatic infiltration, whereas an invasion of the sclera directly has been reported [9,10].

Histopathologic features correlated to increased metastatic progression include a combination of epithelioid type with macrophage/lymphocyte infiltration, increased cell proliferation (mitotic activity) and fibrovascular networks [11]. Based on clinicopathological studies, UM patients with advance T-stage demonstrated high risk for developing metastases, especially in the liver [12]. In the current molecular review, we present specific chromosome numerical and structural aberrations that are implicated in UM genetic substrate and create a variety of genetic signatures in the corresponding patients.

Chromosomal instability in solid malignancies

Gross chromosomal and specific gene alterations are genetic aspects that are involved in its rise, progression and metastatic expansion. Concerning solid tumors, a variety of chromosome and gene functional and numerical imbalances in crucial molecular pathways such as cell cycle regulation, signaling transduction, apoptosis or angiogenesis have been identified and explained.

Chromosomal Instability (CI) is referred to gross chromosome aberrations including abnormal numerical alterations such as0 polysomy –also aneuploidy – (usually 3-5 chromosome copies per nucleus) and monosomy (loss of one chromosome) detectable by karyotyping techniques and fluoresence *in situ* hybridization (FISH) analyses. Furthermore, structural changes and rearrangements (ie translocations) in specific or vast chromosome regions are identified by applying predominantly polymerase chain reaction (PCR) and FISH, especially comparative genomic hybridization (CGH) [13,14].

CI in UM

Concerning UM CI spectrum and rates, specific cytogenetic analyses have revealed a spectrum of numerical and structural alterations implicating predominantly chromosomes 1,3,6,8, and lesser chromosomes 9, 11, 18, and 21, respectively [15]. Chromosome 3 loss (monosomy) –specifically deletions on 3p11–14 and 3p25–26 loci- has been found to be the most frequent karyotypic abnormality correlated to distant metastases in the liver

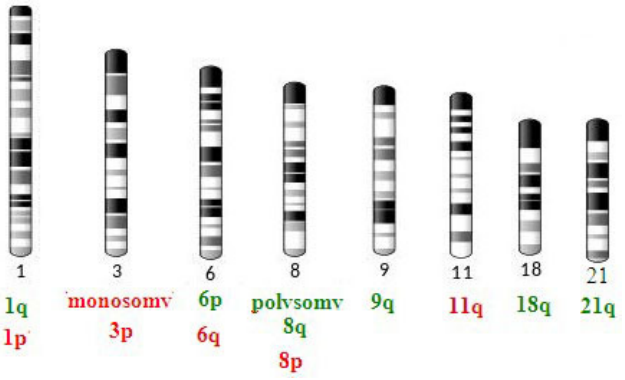

Figure 1. Chromosomal instability (CI) in uveal melanoma (UM). Chromosomes 1, 3, 6, 8, 9, 11, 18, and 21 are involved in UM specific genetic signatures demonstrating gains and losses in p and q axes, or complete monosomy/polysomy (green: gains/polysomy, red: losses/monosomy).

and reduced survival rates [16,17]. Chromosome 6 demonstrates specific gain (6p: 6pt-6p21.2) and loss (6q: 6q16.1- 6q22), whereas only 6q loss has been detected to be involved in UM metastatic potential [18]. Furthermore, chromosome 8 polysomy (mainly trisomy and 8q gain) is also correlated – combined or not with chromosome 3 monosomy- to poor prognosis and distant metastases in the liver [19]. Concerning chromosome 1, deletion of its short (p) arm (1p31 loss) combined with 6q and 8p loss has been observed to correlate to elevated risk for distant metastases and recurrence [20,21]. Interestingly, gains affecting the 1q, 6p, 8q, and 9q and loss of 6q and 11q seem to be associated with PRAME (PReferentially Antigen Expressed in MElanoma) overexpression, which is an independent prognostic biomarker in UMs [22]. Finally, the role of chromosome 18q and 21q loci amplifications -that are present in limited sub-groups of UM patients- remains under investigation [23].

In conclusion, UM represents a distinct histogenetic entity regarding ocular neoplastic lesions. Specific genetic signatures at the level of CI characterize sub-groups of patients affecting the biological behaviour of the tumour leading to aggressive phenotypes (advanced stage-distant metastases, poor response and survival rates), especially combined chromosome 8 polysomy and chromosome 3 monosomy. Besides these aberrations, numerical and structural imbalances in chromosomes 1, 6, 8, 9, 11, 18, and 21 create an extended genetic landscape of genetic signatures in the corresponding patients (Figure 1).

Conflict of interests

The authors declare no conflict of interests.

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