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SPECIAL MOLECULAR REVIEW

Mutational landscape in uveal melanoma

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Summary

Gross chromosomal and specific gene alterations are genetic aspects that are involved in rise, progression, and metastatic expansion of malignancies. Concerning uveal melanoma (UM), 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. UM is the most common primary ocular malignancy demonstrating increased rates, especially in middle-aged white (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) or at the gene mutations status 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). Sporadic or hereditary mediated mutations in genes including BAP1, EIF1AX, GNA11, GNAQ CHEK2, PALB2, SMARCE1, MBD4, MSH6 and MLH1. In the current molecular review, we present specific mutations -as a landscape- that are implicated in UM genetic substrate and create a variety of genetic signatures in the corresponding patients.

Key words: *gene, mutations, ocular, uveal, melanoma, genetics*

Introduction

Concerning non-cutaneous melanomas, uveal melanoma (UM) is the most common of them-although generally rare among all malignancies- demonstrating increased rates, especially in middle-aged white (Caucasian) populations [1,2] In fact, uveal tract and conjunctiva are the main anatomic regions for UM rise and expansion. UM is characterized also by a more aggressive biological behavior compared to conventional cutaneous melanoma. Advanced clinical stage at the time of diagnosis is correlated to poor response to immunotherapy strategies [3]. 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 [4]. 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 conjuncti-

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vitis. 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 [5,6]. 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 [7-9]. Specific UM genetic 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 [10,11].

Critically, identification of specific gene alterations (mutations) - that act as genetic drivers – lead to isolated genetic signatures in the corresponding patients [12]. In fact, genetic substrate leads to histopathologic features correlated to increased metastatic progression including a combination of epithelioid type with macrophage/lymphocyte infiltration, increased cell proliferation (mitotic activity) and fibrovascular networks [13]. Based on clinicopathological studies, UM patients with advance T-stage demonstrated high risk for developing metastases, especially in the liver [14]. In the current molecular review, we focused on genes that are involved in the development and progression of UM creating a landscape of genetic signatures in the corresponding patients.

Genetic alterations in UM

Concerning solid tumors-including UM-, 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 [15]. Chromosomal instability (CI) is referred to gross chromosome aberrations including abnormal numerical alterations such as polysomy -also aneuploidy-(usually 3-5 chromosome copies per nucleus) and monosomy (loss of one chromosome) detectable by karyotyping technique 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) [16,17]. In contrast to CI, changes in genes including point mutations, deletions and amplifications are crucial genetic events that modify their expression leading to altered protein products [18].

Mutations in UM

Extensive cytogenetic analyses in series of UM tissues 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 [19]. Interestingly, specific genetic signatures are correlated with hepatic metastases from UM [20]. Concerning the specific mutational landscape that characterizes the UM substrate, BRCA1 associated protein 1 (BAP1), guanine nucleotide-binding protein G(q) subunit alpha (GNAQ) and guanine nucleotide-binding protein subunit alpha-11 (GNA11) - that act as large GTPases of the Gαq family - represent the main gene loci implicated in its development [21]. BAP1 is located on chromosome 3 (gene locus: 3p21) and its protein product acts as tumor suppressor molecule involved in the regulation of cell cycle, cell differentiation and genomic integrity due to DNA damage repair [22,23]. BAP1 germline mutations are associated with a high familial predisposition not only for UM development, but also for other malignancies including renal cell carcinoma, cutaneous melanoma (combined with p16 alteration) and mesothelioma [24]. Additionally, loss of wild type BAP1 or a truly defined germline mutation is implicated in the onset of other syndromes considered second primary neoplasms in patients with UM [25]. Concerning GNAQ and GNA11 genes, their activating mutations are correlated to BAP1 deregulation - as early genetic alterations - combined with CYSLTR2/PLCB4 mutated genes [26,27]. Furthermore, other genes, such as Splicing factor 3b, subunit 1 (SF3B1) and eukaryotic translation initiation factor 1A (EIF1AX) have been found to be mutated in UMs associated with well differentiated neoplasms demonstrating better prognosis compared to the previous referred BAP1 - depended on UMs [28,29]. Additionally, a spectrum of cancer-related genes in solid malignancies have been also indirectly related to UMs, including BRCA2, BRCA1, CHEK2, PALB2, SMARCE1, MBD4, MSH6 and MLH1 [30,31]. Furthermore, recently published studies focused on specific microRNAs (miRs) as valuable micro-genetic markers implicated in proliferation, apoptosis and signalling transduction pathways in UM patients [32,33].

In conclusion, UM is characterized by a variety of chromosome and gene functional and numeri-

cal imbalances in crucial molecular pathways such as cell cycle regulation, signaling transduction, apoptosis or angiogenesis which have been identified and explained. Sporadic or hereditary mediated mutations in genes including BAP1, EIF1AX, GNA11, GNAQ CHEK2, PALB2, SMARCE1, MBD4, MSH6 and MLH1 create a broad mutational landscape implicated in UM pathogenesis leading to specific genetic signatures in the corresponding patients.

Conflict of interests

The authors declare no conflict of interests.

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