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Review

Overview of BAP1 cancer predisposition syndrome and the relationship to uveal melanoma

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Abstract

Purpose: The aim of this study was to review the genetics, epidemiology, clinical findings, and management of BRCA1-associated protein-1 (BAP1) cancer predisposition syndrome, particularly focusing on the development of uveal melanoma (UM).
Methods: This is a review article based on eligible studies identified by systematically searching PubMed, Web of Science, and reference lists.
Results: UM is the most common primary intraocular malignancy. Most UM cases are sporadic, but a small percentage has been documented with familial tendency. Until recently, there was little information regarding the genetics of this malignant tumor, and we have now begun to understand the pathways of development. BAP1 is a scavenger protein that regulates cell cycle, cellular differentiation, and DNA damage response. Patients and families with germline BAP1 mutation are predisposed to familial cancers including UM, mesothelioma, cutaneous melanoma (CM), renal cell carcinoma (RCC), and others. Clinicians should be aware of the implications of germline BAP1 mutation and advise genetic testing and assessment for BAP1 germline mutation in suspected patients and families.
Conclusions: The ability of BAP1 gene mutation to cause multiple tumor types and high penetrance in carriers suggests that this gene has an important role for influencing cancer cell growth. With progress in understanding the molecular landscape of UM and the development of treatments targeted to the pathways involving BAP1 and other gene mutations, it is possible to improve the outcome of this malignant cancer.

Keywords: Uveal melanoma; Mesothelioma; Renal cell carcinoma; BAP1 cancer predisposition syndrome; BRCA1-associated protein-1; BAP1

Introduction

Uveal melanoma (UM) is the most common primary intraocular malignancy in adults and most commonly found in light complexion Caucasians with an age-adjusted incidence of 4.3 per million people.[1–3] It is estimated that approximately 2500 North Americans develop UM annually.[1] While the disease is relatively rare, the chance for two or more first-degree relatives with UM is exquisitely low, estimated to be less than 0.0002.[4] However, approximately 1% of all UM patients demonstrate some degree of familial uveal melanoma (FUM),[5,6] and it has been suggested in the past that there could be an autosomal dominant (AD) mode of inheritance for familial form of UM.[4]

Since 1971, several reports have described the association between UM and other cancers,[7] especially cutaneous melanoma (CM), breast cancer, and prostate cancer.[8–10] Abdel-Rahman et al estimated that approximately 11.6% of all patients with UM are at risk for a hereditary cancer predisposition.[5] In a prospective analysis of 2320 cases of UM in the Collaborative Ocular Melanoma Study (COMS), second cancers were found in 222 (10%) patients, excluding basal or

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squamous cell carcinoma. The most common second malignancies were cancer of the prostate (2.2%), breast (1.6%), lung (1.2%), genitourinary (1%), gastrointestinal (0.9%), and leukemia/lymphoma (0.8%). In that cohort, the 5-year cumulative risk for second primary cancer was 8% at 5 years and 15% at 10 years.[10]

Patients with hereditary predisposition to UM could have higher risk for development of other cancers related to germline genetic alterations. In a 1996 analysis of FUM in 27 families from our department, we concluded that most affected patients were first-degree relatives, and underlying genetic alterations, yet to be discovered, were likely responsible for this relationship.[4] Since then, now over 20 years later, genetic alterations important for UM development and progression have been identified and include Guanine nucleotide-binding protein G (GNAQ/11), Eukaryotic translation initiation factor (EIF1AX), Splicing factor 3B subunit 1 (SF3B1), and BRCA1-associated protein-1(BAP1).[11,12]

BAP1 is a highly-penetrant germline mutation that has been recognized as an important predisposing factor for hereditary cancers, including UM.[12] BAP1 tumor predisposition syndrome (BAP1-TPDS) is a newly-recognized cancer syndrome that predisposes the patient to UM, malignant mesothelioma (MMe), CM, renal cell carcinoma (RCC), and possibly to a range of other cancers as well.[12–14] Compared to non-predisposed patients with equivalent cancers, most of the BAP1-related cancers tend to be more aggressive and triggered earlier in life.[13,14] Therefore, patients with BAP1 germline mutation are at risk for several malignant tumors and should be counseled regarding cancer risk for patient and family members as well as routinely monitored.

BAP1 gene structure and function

BAP1 is a deubiquitinating enzyme, with the gene located on the short arm of chromosome 3 (3p21.1), and contains 729 amino acids.[14,15] This protein has three main domains including N-terminal catalytic domain, which removes ubiquitin from ubiquitylated substrates; the middle portion with host cell factor 1 (HCF1) binding domain; and the C-terminal domain (CTD) which is important for interaction with additional sex combs like (ASXL1/2) and other proteins.[14] (Fig. 1).

BAP1 functions as a tumor suppressor protein through its deubiquitinase activity that regulates target genes in cell cycle control, cellular differentiation, and DNA damage repair. This protein has been shown to form a ternary complex with HCF1 and transcription factor Ying Yang 1 (YY1) for cell proliferation and cell cycle control.[15] BAP1 is an essential DNA damage repair enzyme, through a complex with several recombination proteins including Breast Cancer type 1 (BRCA1) and BRCA1-associated RING domain protein 1 (BARD1), which promotes E3 ubiquitin ligase activity to regulate DNA damage response.[14] The first reports demonstrated that tumor suppressor effect of BAP1 results from nuclear localization and deubiquitinating activity,[15] but new findings revealed that extra-nuclear BAP1 was specifically present in the endoplasmic reticulum (ER) fraction. It binds, deubiquitylates, and stabilizes type 3 inositol-1,4,5-trisphosphate receptor (IP3R3), modulating calcium release from the ER into the cytosol and mitochondria, promoting apoptosis.[16] Nevertheless, the structural architecture of the details of BAP1 complexes have not been completely characterized, so the impact of various mutations is still unclear.[14,15]

History and epidemiology

BAP1 is a deubiquitinating hydrolase enzyme that was identified in 1998, and initial data suggested that BAP1 suppressed the growth of human breast cancer cells in soft agar.[17] Earlier reports had shown that BAP1 tumor suppressor function was in cooperation with BRCA-1 in cultured cells, so this enzyme was initially named BAP1, but later shortened to BAP1.[17] Over a 10-year period, the true clinical value of the impact of BAP1 was realized.

Some of the understanding of BAP1 came through clinical observations of familial cancers.[4,5] One sentinel example is the story of familial mesothelioma. MMe in the western world is often associated with asbestos exposure.[18] This is a relatively rare cancer causing 2500 deaths yearly in the United States. In contrast, in Cappadocia, a semi-arid region in central Turkey, a mesothelioma epidemic was observed in the early 2000s.[18] Among people living in 3 small villages, 50% of all deaths were caused by this malignant tumor.[18,19] Pedigree studies of these villages revealed that mesothelioma was prevalent in some families but not others, and this malignancy was transmitted in an AD fashion.[18,19] At the same time, in the United States, two unrelated families, L (from Louisiana) and W (from Wisconsin), were found with high incidence of mesothelioma, and each had only minimal exposure to asbestosis.[20] Further important clinical observations disclosed that two members in the L family developed UM.[20] In the United States, approximately 3000 patients with mesothelioma and 2500 patients with UM are diagnosed annually; hence, chance for simultaneous occurrence of these rare malignancies in more than one individual in the same family was estimated at 36 per trillion population.[20] This linkage suggested a common genetic factor. Genetic assessment and chromosome microarray on the L and W families disclosed alteration in chromosome region 3p21 in both mesothelioma and UM cases.[20] Sequencing this region of chromosome 3 led to the identification of germline BAP1 as the mutated gene in the L and W families.[21] Since then, mutations in BAP1 gene has been confirmed in mesothelioma,[20] UM,[21] CM,[22] and RCC.[23]

BAP1 tumor predisposition syndrome

BAP1 tumor predisposition syndrome (BAP1-TPDS) is a novel cancer syndrome that has been identified from three independent research groups, initially focusing on mesothelioma, CM, and UM.[20–22] Shortly afterward, RCC was included this group.[23] The molecular mechanisms and cellular pathway responsible for leading to specific tumor types, and the difference in disease outcomes remain unclear.[14] The full

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