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BAP1 Immunostaining in Uveal Melanoma: Potentials and Pitfalls

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BRCA1-associated protein-1 (*BAP1*) is a tumor suppressor gene located on the short arm of chromosome 3 (p21.1). It is involved in cell cycle regulation, transcription, DNA damage repair, and chromatin dynamics.

Recently, its prognostic role in uveal melanoma (UM) has been further elucidated by several independent groups showing that somatic *BAP1* mutations are associated with a higher risk for metastasis [1–5]. While genetic testing is expensive and time-consuming, immunohistochemical staining can be easily performed on formalin-fixed paraffin-embedded tissue, and was therefore proposed as a good alternative [3]. Several commercially available antibodies targeting BAP1 are offered by different companies. However, in most studies the antibody from Santa Cruz Biotechnology, Dallas, TX, USA (clone sc-28383) is used.

Several studies have shown promising results, in particular an excellent correlation of BAP1 immunostaining with genetic analysis (although in some cases discrepancies were observed) [1, 3, 4], as well as the identification of a subgroup of "atypical" poor-prognosis disomy 3 patients [2]. Thus, BAP1 immunohistochemical screening was suggested as the routine staining for UM molecular work-up [2, 3].

Laboratories working with this antibody are aware not only of the benefits of BAP1 immunostaining but also of its pitfalls. While nuclear staining is associated with intact BAP1 function and a low risk for metastatic disease, an absent BAP1 nuclear signal, as well as cytoplasmic staining, is associated with a worse prognosis and a higher probability for metastases, in particular to the liver. The problem with this is the fact that the quality of an immunohistochemical staining reaction always depends on several factors such as the time of fixation and storage in paraffin. As some laboratories [pers. commun.] had difficulties in obtaining reliable and qualitatively good staining results, we would like to mention that an internal control – besides an appropriate positive and negative control – is mandatory to verify the staining reaction in every specimen investigated. For this purpose, nuclear BAP1 expression in retinal cells, inflammatory cells, or intratumoral vessels can be used [1, 4]. In the absence of such an internal positive control, it is difficult to assess the reliability of BAP1 nuclear expression in a tumor. In our experience, factors which influence BAP1 immunostaining are mainly the age of tissue (in particular if it is older than 20 years) and old slides (not freshly cut tissue). In such cases, the application of a "linker" (EnVision™ FLEX+ system; Dako, Glostrup, Denmark) may be helpful to enhance the immunohistochemical signal. In heavily pigmented cases, a bleaching procedure after incubation with the antibody might also be helpful, as well as the application of a red chromogen (e.g., 3-amino-9-ethylcarbazole).

Taking the benefits and the drawbacks into account, BAP1 immunostaining is a useful method to stain paraffin-embedded tissue in the presence of an appropriate internal positive control and may be further implemented as a routine marker for UM in the hands of an experienced ophthalmic pathologist, as suggested by others before. Its prognostic role also justifies further studies of *BAP1* in UM pathogenesis. In equivocal cases, genetic analysis of the tissue for *BAP1* status is still recommended. In addition, based on our experience in Bonn, particular attention should be given when staining archival tissue for retrospective studies, since in those cases BAP1 immunostaining results might be difficult to interpret.

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