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Evaluation of Bcl2-associated agonist of cell death (BAD) as a prognostic biomarker in Sonic Hedgehog-driven medulloblastoma

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The aim of this thesis was to analyze the value of various proteins as a potential prognostic biomarker in medulloblastoma. Therefore, the results from gene expression databases were combined with immunohistochemical and statistical analyses. It was found that low expression of bcl2-associated agonist of cell death (BAD) mRNA, a key mediator of apoptosis, is associated with poor overall survival (OS) in Sonic hedgehog medulloblastoma (SHH-MB). Conversely, BAD protein expression was associated with poor OS in the same cohort. These contradictory results point towards the possibility that BAD functions differently than its well documented role in apoptosis and might be crucial for tumor homeostasis in SHH-MB. When SHH dependent cells are exposed to environmental stress they switch on a cellular survival program named autophagy that includes digestion of large intracellular vesicles and protein aggregates to provide metabolites to produce energy. BAD protein supports autophagy through inhibition of bcl2. Phosphorylation of BAD on Serin 136 inactivates this function. Therefore, the cohort was analyzed for the expression of p-BAD. It was found that the presence of p-BAD was significantly associated with overall survival independent of age, gender, histologic subtype, surgical resection status, presence of TP53 mutations and presence of metastases. Therefore, this thesis shows that phosphorylation of BAD prevents autophagy and therefore the SHH-MB cell to adapt to stress conditions, thus making immunostaining for p-BAD a valuable prognostic biomarker in SHH-MB since it its expression is significantly associated with high overall survival.
However, several difficulties necessitate further analyses: Specificity of the antibodies used for the laboratory work needs to be assured and proved for realibility Moreover, since the investigated cohort was rather small and the use of immunohistochemistry for the evaluation of potential biomarkers may be associated with technical susceptibility to interferences, the results shown have to be interpreted with some caution. Further studies in larger patient cohorts and with more customized antibodies are thus needed to definitely clarify the role of BAD/p-BAD in SHH-medulloblastoma.