Loss of MTAP expression ~~indicates~~ is associated with poor prognosis in ~~less overall survival in~~ glioma patients

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BACKGROUND: Gliomas are the most common primary brain tumors in adults, affecting about 4.000people in the Brazil each year. Genomic studies have shown frequent deletion of 9p21 region in gliomas, harboring the well-known tumor suppressor gene *CDKN2A*/*ARF*. It has been reported that other important genes can be deleted in this region, and recent studies, including from our group, showed that *MTAP* (Methylthioadenosine Phosphorylase) deletion could also contribute to gliomas tumorigenesis. *MTAP* regulates the purine salvage pathway where it catalyzes MTA. The products of the reaction are adenine and MTR-1-P.Loss of MTAP has been reported in other solid tumors, and due to its function it can be used for therapeutic strategies. Our aim was to evaluate the MTAP expression in gliomas, and correlate it the clinico-pathological features of the patients. METHODS: We used western blot and qRT-PCR to investigate *MTAP* expression in18 human adult and pediatric glioblastoma cell lines and compared with gene copy number alteration. By through immunohistochemistry, we assessed MTAP protein expression in a series of 597 gliomas (WHO grade I to IV) and correlated with patient's clinico-pathological features. Moreover, in a subset of cases, the immunohistochemistry results were correlated with gene expression levels (qRT-PCR) and array-CGH. RESULTS: Absence of MTAP gene/protein expression was found in 33% (6/18) of glioblastoma cell lines. Immunohistochemistry ~~When comparing the gene expression of the *MTAP* expressing cell line vs. 102 patients tumors, we found that the expression was 75% lower (p=0.001). l~~Loss of MTAP expression was observed in ~~overall~~ 46% of ~~the 597~~ gliomas, and specifically ~~in~~ in 16% of~~cases analyzed. Specificatlly,~~ low grade gliomas (WHO I and II) ~~showed 16% of loss~~and 51% of ~~, and~~ high grade gliomas (III and IV) ~~displayed 51% loss~~ (P<0.001). ~~Importantly, we~~We observed a better overall survival correlated to positive MTAP expression in gliomas (p=0.007). In the subset of gliomas with DNA/RNA and protein data, w~~W~~e observed a correlation between ***MTAP*** gene deletion (array-CGH), ~~loss~~ downregulation of gene expression (qRT-PCR) and protein (IHC) absence ~~in gliomas~~. CONCLUSIONS: ~~In this study~~This is the larger study of MTAP alterations in gliomas. Loss of MTAP expression was associated with increased tumor malignancy, and overall worse outcome. ~~we report in a large series of glioma the expression profile of MTAP gene/protein, and that patients with loss of MTAP expression show lower overall survival when compared with patients that express MTAP. These data were also observed in GBM cell line, can be used specific target cell therapy. Further studies are needed to extend and validate these findings and determine its clinical-pathological impact.~~