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Loss of MycBP may be associated with the improved survival in 1P co-deletion of lower grade glioma patients

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ABSTRACT

Objectives: The chromosome 1p/19q co-deletion is a favorable prognostic factor in patients with low grade glioma. In the current analysis, we examined MycBP expression in low grade glioma. MycBP lies on chromosome 1p.

Patients and methods: We evaluated the association between MycBP and overall survival in the TCGA Lower Grade Glioma (LGG) dataset in TCGA (The Cancer Genome Atlas).

Results: Loss of MycBP copy number segment expression coincides with co-deletion of 1 P. The deleterious effect of MycBP on survival is significant (p = 0.00006306, hazard ratio 2.02, 95% CI 1.4–2.9). Patients with astrocytoma have the poorest survival of low grade glioma patients. MycBP mRNA is significantly overexpressed in astrocytomas when compared to normal brain (2.156 fold change, p = 0.0000488).

Conclusion: Our report that Chromosome 1 P co-deletion may confer better survival in patients with lower grade glioma in part because of loss of MycBP corroborates other studies of the importance of MycBP in glioma development. Further work with microRNAs may lead to new treatments.

1. Introduction

Lower grade glioma is a lethal neoplasm of young adults with death occurring after approximately 7 years. Although lower grade glioma patients do better than patients with high grade glioma (WHO grade III/IV), a majority of lower grade gliomas become fatal high grade gliomas. The Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute indicates that lower grade glioma patients' grim outlook has not improved in the past thirty years [1].

The prognosis of lower grade gliomas has traditionally been determined by histologic type and histologic grade. Astrocytomas have a worse prognosis than oligoastrocytomas or oligodendrogliomas. Grade 3 lower grade gliomas have a worse prognosis than grade 2.

More recently, molecular markers have been studied [2]. From best prognosis to worst they can be ranked as follows:

- lower grade gliomas with isocitrate dehydrogenase (IDH) mutation and chromosome 1p/19q codeletion (best prognosis).
- lower grade gliomas with IDH mutation and no 1p/19q codeletion.
- lower grade gliomas with wild-type IDH (worst prognosis).

Variations of IDH1/2, ATRX, TERT, TP53, and co-deletion of 1p/19q allow segregation of gliomas into subsets [3]. Patients with lower-grade gliomas, an IDH mutation and 1p/19q codeletion frequently have mutations in CIC (19q13.2), NOTCH1 (9q34.3), the TERT promoter (5p) and FUBP1 (1p31.1) [2].

Chromosome 1 is the largest human chromosome, over 3000 genes, 240 million base pairs, of which ~90% have been determined, representing 8% of human DNA. Approximately 890 diseases are linked to chromosome 1 gene mutations. Among them are cancer, Parkinson's disease and Alzheimer's disease, as well as glaucoma and deafness [4].

The Myc gene on chromosome 8q24 codes for a transcription factor that plays a role in multiple human cancers, and Myc expression correlates with glioma grade. Annibali et al have recently reported that Myc inhibition is effective against glioma; Myc is important for proficient mitosis [5].

Myc is in fact not a single gene but a family of genes [6]. Of this family, one member, MycBP, the Myc binding protein, resides on chromosome 1p (1p33-p32.2). Overexpression of MycBP (also called AMY-1) increases the malignancy of gastric cancer [7].

In the current analysis, we examined MycBP expression in lower grade glioma.

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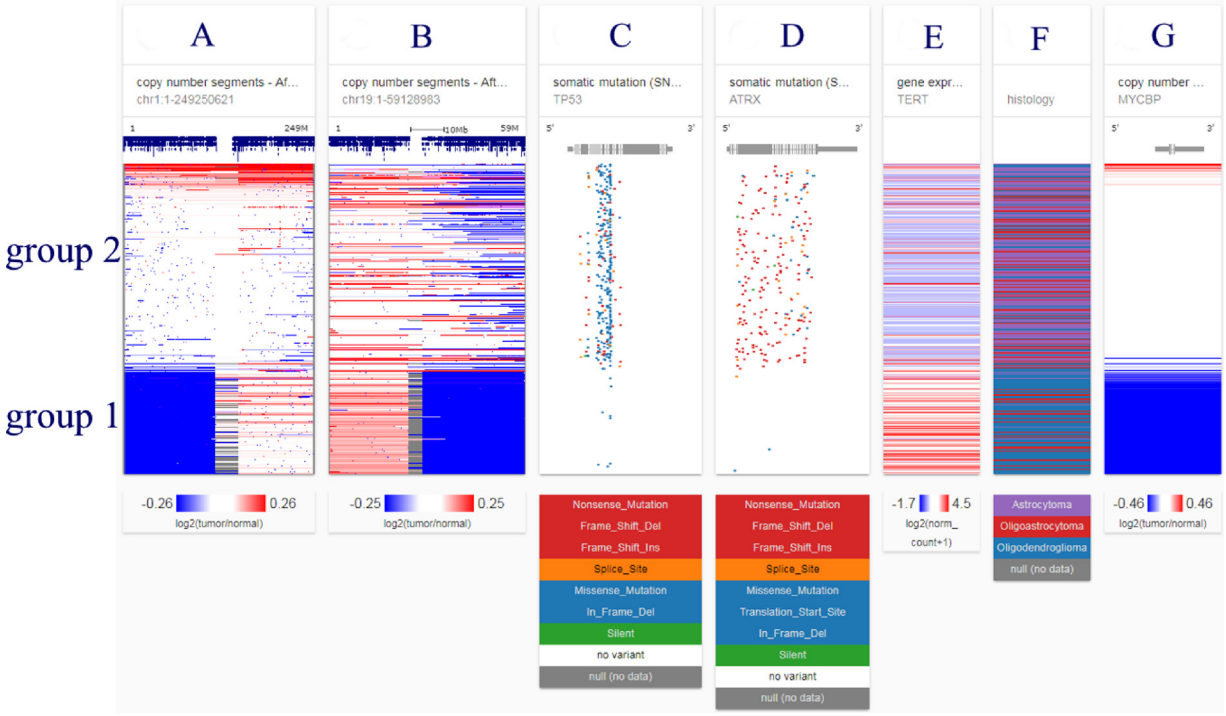

Fig. 1. Genetic separation of lower grade gliomas into two disease groups in 536 patients studied. Group 1 is characterized by loss of chromosome arms 1p and 19q (blue blocks, columns A and B) and TERT over-expression (column E); group 2 by TP53 and ATRX mutations (columns C and D). Loss of MycBP is indicated by loss of copy number segment expression (blue block, column G) and coincides with co-deletion of 1 P. Astrocytoma (column F) falls into group 2, the poorer prognosis group. Each row contains data from a single sample. Row order is determined by sorting the rows by their column values (UCSC Xena http://xena.ucsc.edu).

2. Patients and methods

We evaluated the association between MycBP and overall survival in the TCGA Lower Grade Glioma (LGG) dataset in TCGA (The Cancer Genome Atlas). To access and analyze data we used:

- Genomic Data Commons Data Portal (https://portal.gdc.cancer.gov)
- UCSC Xena browser (https://xenabrowser.net). UCSC Xena is a web-based visual integration and exploration tool. The investigator-driven platform consists of a web-based Xena Browser which permits cancer analysis of genomics datasets from TCGA, Pan-Cancer Atlas, PCAWG, ICGC, GTEx, and the GDC; a total of more than 1500 datasets across 50 cancer types (8). The Xena browser generated Figs. 1 and 2 from TCGA data. SPSS generated Fig. 4 with data downloaded from the Xena browser.
- Oncomine (https://oncomine.org) database is an online collection of microarrays from various sources, usually cancer-related, and contains many *multi-arrays* (collections of analyzed microarrays, in a single study). There are often many hundreds of tumour samples/microarrays within a single multi-array. Results from coexpressed genes can be analyzed, and are fully searchable [9]. The Oncomine database generated Fig. 3 from published data [10].

Survival data of the glioma subgroup were extracted for analysis and generation of Kaplan–Meier curves for overall survival.

3. Results

We analyzed data from 536 patients with lower grade glioma. The patients' mean age was 43 ± 14 (mean ± SD). 55% of the patients were male, 45% female. 92.1% were white, 4.1% African-American, 1.6% Asian, 0.2% American Indian or Alaska native, 1.9% unclassified. Mean survival was 7.8 years.

Genetic separation of lower grade gliomas into two disease groups in 536 patients studied is shown in Fig. 1. Group 1 is characterized by loss of chromosome arms 1p and 19q (blue blocks, columns A and B) and TERT over-expression (column E); group 2 by TP53 and ATRX mutations (columns C and D). Loss of MycBP is indicated by loss of copy number segment expression (blue block, column G) and coincides with co-deletion of 1 P. Patients with astrocytoma have the poorest survival of low grade glioma patients. Astrocytoma (column F) falls into the second, poorer prognosis, group. Each row contains data from a single sample. Row order is determined by sorting the rows by their column values.

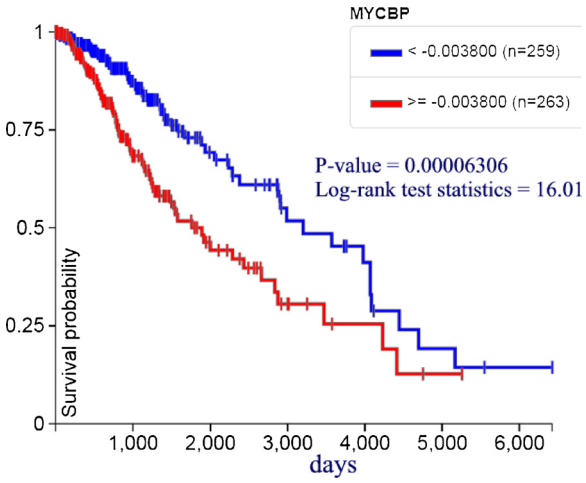

Fig. 2. Survival probability versus MycBP copy number segments. The effect is significant (p = 0.00006306, hazard ratio 2.02, 95% CI 1.4–2.9). Numbers written beside the blue and red bars are cut-off values.

Survival probability versus MycBP copy number segments is shown in Fig. 2. The deleterious effect of MycBP on survival is significant (p = 0.00006306, hazard ratio 2.02, 95% CI 1.4–2.9). Increased MycBP

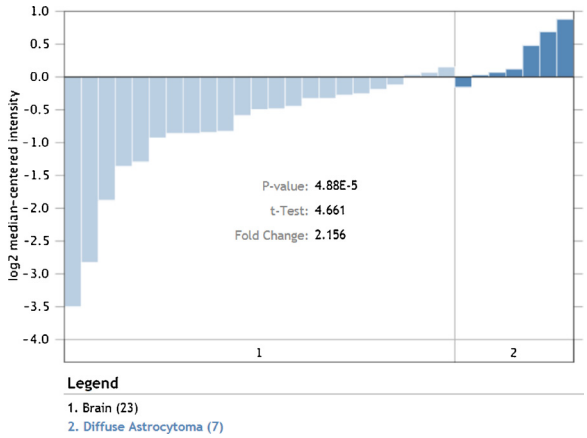

Fig. 3. MycBP mRNA is significantly overexpressed in 7 diffuse astrocytomas when compared to 23 normal brain samples (2.156 fold change, p = 0.0000488) (https://oncomine.org, data from Sun et al, Cancer Cell 2006).

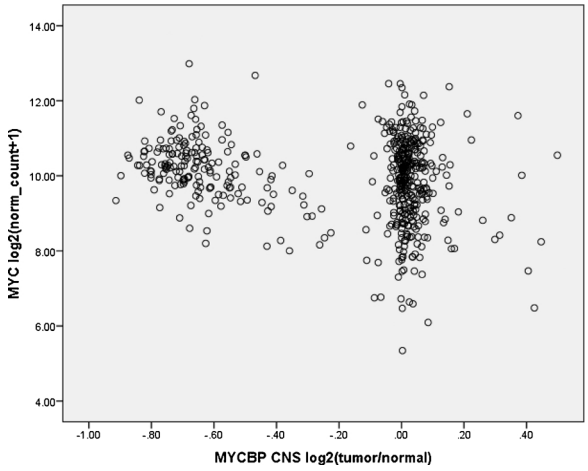

Fig. 4. MycBP copy number segments versus MYC gene expression.

expression is strongly related to poor survival. The survival endpoint is arbitrarily set at 6500 days. The optimal cutoff was identified by methods described in the R2 web-based application (http://r2.amc.nl)); the method divides the sample, ascending order gene expression, into equal-sized groups, in this case 259 tumors with fewer copy number segments, 263 tumors with more copy number segments. Further details have been published [11].

MycBP mRNA is significantly overexpressed (log 2 median centered intensity) in astrocytomas when compared to normal brain (2.156 fold change, p = 0.0000488, Fig. 3) [10]. Median centering is used in Oncomine to reduce the bias that can be introduced by tissue types [12].

Fig. 4 shows MycBP copy number segments versus MYC gene expression. Note that the data points cluster in two groups. Apparently, when MycBP function diminishes sufficiently, MYC is somehow able to resume expression, which had stopped during the mid-range of MycBP activity.

4. Discussion

MycBP encodes a protein that binds to the N-terminus of C-MYC, enhancing the ability of C-MYC to activate E box-dependent transcription. E-box enhancers regulate gene expression in neurons, muscles, and other tissues. The encoded protein is normally found in the cytoplasm, but it translocates to the nucleus during S phase of the cell cycle and associates with C-MYC. Two MycBP transcript variants, one protein-coding and the other probably not protein-coding, have been found [13]. MycBP can be silenced by microRNA-22, suggesting a possible therapeutic intervention.

MycBP (AMY-1) is involved in glioma proliferation [14]. MycBP has been identified to be a coactivator of c-Myc, which is known to contribute to cell cycle progression, transformation, and apoptosis as an oncogene [15]. In gliomas, c-Myc proto-oncogene expression correlates with grade of malignancy: low expression in Grade I and II and high expression in Grade III and IV gliomas [16].

One therapeutic option in lower grade glioma could be microRNAs (miRs), which affect cell growth and function. Several reports have demonstrated that one microRNA, miR-139, inhibits growth of multiple solid tumor types via different pathways. Although the antitumor mechanisms of miR-139 are not well understood, Wang et al have demonstrated the low expression level of miR-139 in glioma tissues and cell lines. Moreover they have shown miR-139 to retard glioma development and invasion both in vitro and in vivo by inhibition of MycBP [14].

The identification of a validated miRNA signature could be useful in predicting patient outcomes and tailoring treatment regimens for glioma. However, the proposed antitumor activity of MiR-139 has not been well-studied nor clarified. The prognostic value of a seven-microRNA classifier as a novel biomarker for the prediction and detection of recurrence in glioma patients could have important implications [17].

Our study has some limitations. Although loss of MycBP corroborates other studies of the importance of MycBP in glioma development, the precise influence of this gene on glioma development is not yet well clarified. In this paper we only present the information that Chromosome 1p co-deletion may confer better survival in patients with lower grade glioma and MycBP may have a deleterious effect on survival.

Our report that Chromosome 1 P co-deletion may confer better survival in patients with lower grade glioma in part because of loss of MycBP corroborates other studies of the importance of MycBP in glioma development. But our results in terms of survival have not been correlated with the different treatments performed (surgery, extent of resection, radio and chemotherapy). Further studies of treatments, particularly microRNAs, may lead to new forms of therapy.

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Conflicts of interest

None.

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