Genomic evolution of a human glioma stem cell line in an orthotopic GBM mouse model

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Glioblastoma multiforme (GBM) is the most frequent and lethal malignant brain tumor, as patients die within 15 months after diagnosis. The failure of current therapies is ascribed to a subpopulation of cells with stem-like properties, called glioma stem cells (GSCs). Given the high malignant nature of GBM and the failure of existing therapies, preclinical models that recapitulate both histopatological and molecular human GBM features are essential for the identification of signal pathways involved in tumor initiation, progression and resistance to therapeutic treatments.

In this study we characterized the orthotopic xenograft model established by GSCs injection into NOD/SCID mice. We firstly investigated the expression of stemness markers by immunohistochemistry (IHC) on formalin fixed paraffin embedded (FFPE) tissues and by immunofluorescence (IF) on the correspondent cell line. Then, in order to assess whether in the animal injected orthotopically with GSCs there was a selection of a specific subpopulation, we performed array-CGH on the DNA extracted from GSCs and from the FFPE tissues of the xenograft mouse model.

We found that IF and IHC showed a perfect correspondence for stemness markers expression. DNA from GCSs and ex vivo tissues shared many alterations, as complete loss of chromosome 6 and q arm of chromosome 15, the alterations found on chromosome 12 and the gain of chromosome 7. However, we also found interesting differences between the samples; for instance, the loss of the region of TP53 locus (chromosome 17p13.1) in the ex vivo tissues while its locus is not affected by any alterations in GSCs. Moreover, the alterations found in chromosome 19 are completely different between the samples: a gain of its p and q arm, which harbour Notch3 and Bax loci respectively, in GSCs, and loss of a small region in the p arm in the ex vivo tissue.

We conclude that in the animal model there was a selective pressure due to the microenvironment that brought to a genomic evolution of a subpopulation of cells with different copy number features compared to the naïve GSCs. The generation of GBM orthotopic models from GSCs could help in better characterizing the genomic and molecular changes that occur when GSCs find themselves to be in a new environment.