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Tracking glioma progression by genetic barcoding

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During tumor progression, transformed cells accumulate mutations and gain malignancy. By now, it is unclear how easily this process can be undertaken and if it can be considered the main bottleneck in tumorigenesis. To measure the probability of glioma progression, we used a well-characterized murine model of gliomagenesis, induced by overexpressing PDGF-B in embryonic Neural Progenitor Cells (NPC), mimicking a possible first hit of tumorigenesis. In order to univocally tag each PDGF-transduced cell, we added a degenerated barcode sequence to the PDGF-B transducing vector and we produced high complexity libraries of barcoded retroviruses that had been injected in mouse embryos. After the development of gliomas, tumor masses were analyzed by NGS and compared to embryonic brains few days post infection. By using in-house developed software, we successfully retrieved barcodes from tumor masses and reconstructed the clonal composition of several independent tumors in different progression stages. Our data shows that even though low grade, partially progressed tumor masses are clonally heterogeneous and composed by about one thousand independent clones each, they are the result of a strong selection because the number of oncogene-transduced cells is more than 10 times higher. Still, high grade and fully progressed gliomas are characterized by a very low clonal complexity and often are composed by a single clone, suggesting another great bottleneck in glioma progression divides these two stages. More strikingly, fully progressed tumors derived from *in vivo* transplant the same pool of thousands different transduced NPCs are composed by the same clones, suggesting that a predetermined cell state is required to gain malignancy.

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