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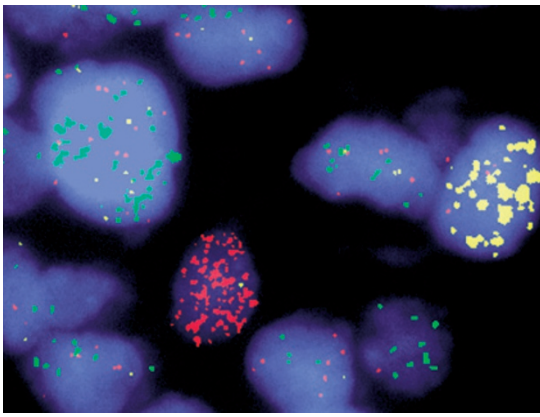
GENETICS

United colors of glioblastoma

Glioblastoma multiforme (GBM) is the most common and aggressive brain tumor in adults, and it is very difficult to treat as it is resistant to most conventional therapies, probably due to its heterogeneous nature. Tumorigenesis of GBM is commonly driven by gene amplification of tyrosine kinase receptors (RTKs), with 50% of GBM showing amplification of a RTK, including *EGFR, PDGFRA* and *MET*.

For several years John Iafrate and his team have focused on the clinical genotyping of human tumors to try to provide tailored targeted therapies to patients with cancer and, in their latest work, they have investigated RTKs as possible therapeutic targets in GBM. They were also interested in assessing the heterogeneity of gene amplification events occurring in RTKs in these tumors.

To that end, they analyzed 350 samples of GBM with multicolor fluorescence *in situ* hybridization, which allows simultaneous detection of three genes, in this case *EGFR, PDGFRA* and *MET,* in single tumor cells. Of the samples analyzed, 16 had more than one amplified RTK. Twelve tumors had two different subpopulations—each one showing gene amplification of only one of the RTKs—and four tumors showed subpopulations with mutually exclusive amplification of all three genes. All the different subpopulations shared the presence of a mutation in *TP53* and *CDK2A* suggesting that they were subclones derived from an unique precursor rather than independent tumors. "This [work] describes, surprisingly, that multiple genes in the same class (RTKs) can be activated in adjacent intermingled cells," says Iafrate. "We knew, going into the study, that RTKs are important drivers in GBM. We assumed, however, that only one would be active in any given tumor. These data indicate that tumors can be mosaics, made up of multiple clones with distinct genetic lesions, which may require combination of kinase inhibitors to be eradicated. The presence of such mosaics also suggests the interesting possibility that tumor cell populations may sub-specialize, and perhaps provide mutual growth support to one another".



Three subpopulations of GBM cells with mutually exclusive amplification of EGFR (red), MET (green) and PDGFRA (yellow). Courtesy of A. J. Iafrate.

Further studies on genetic mosaicism and combination of RTK inhibitors will help in understanding the implications of these observations in cancer therapy.

M. Teresa Villanueva

Original article Snuderl, M. *et al.* Mosaic amplification of multiple receptor tyrosine kinase genes in GBM. *Cancer Cell* **20**, 810–817 (2011)