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COMMENTARY

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ERBB3 as a therapeutic target in glioblastoma: overexpression can make the difference

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ABSTRACT

By exploiting an integrated experimental platform based on patient-derived cancer stem cells, we identified a glioblastoma subset characterized by inheritable Erb-B2 Receptor Tyrosine Kinase 3 (ERBB3) overexpression, metabolic dependency on ERBB3 signaling, and liability to ERBB3 targeting. We provide insights on why some glioblastomas may rely on ERBB3 and how to recognize them.

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Glioblastoma (GBM), the most frequent brain tumor, is almost invariably lethal in spite of aggressive multimodal therapies. Extensive genetic and molecular characterization has significantly impacted on disease taxonomy[1] but, so far, it has provided limited hints for targeted intervention. In spite of failures, a prerequisite to identify effective therapeutic targets remains to recognize the molecular mechanisms selected during tumorigenesis and essential for sustaining cell proliferation and survival. A landmark finding has been that GBM, as many other solid tumors, contains a cell hierarchy headed by cancer stem cells (hereafter indicated as glioblastoma stem cells, GSC). GSCs are endowed with self-renewal and long-term propagation ability, and display unique tumor-initiating activity in experimental settings, together with pseudo-differentiation ability.[2,3] Most importantly, GSCs were shown to be proficient in efficiently repairing DNA damage after treatment with conventional therapies, thus fostering GBM recurrence.[3] These observations imply that, to eradicate a tumor, it is mandatory to identify and target mechanisms that regulate GSC homeostasis.

To this end, we generated a cohort of 84 cultures enriched in GSCs and propagating as floating neurospheres (NS), which faithfully retain the genomic landscape and the transcriptomic profiles of their matched original tumors, and reliably recapitulate their genetic and phenotypic features upon transplantation in the mouse. In this cohort, we observed that approximately 9% of NS are characterized by marked Erb-B2 Receptor Tyrosine Kinase 3 (ERBB3) overexpression (Figure 1).[4] ERBB3 belongs to the Epidermal Growth Factor Receptor (EGFR) family, encompassing 4 members that get activated upon ligand-induced homo- or heterodimerization. ERBB3, although capable of ligand binding, has a defective kinase domain and can be activated only by heterodimerization. As a rule, the latter occurs with another EGFR family member,[5] but it can also involve other receptor tyrosine kinases, mostly the Hepatocyte Growth Factor Receptor (HGFR, encoded by the MET oncogene).[6] When phosphorylated, ERBB3 displays a peculiar ability to sustain Phosphatidylinositol 3-Kinase (PI3K)/AKT pro-survival signaling, which can contribute to resistance against conventional and targeted therapies, and to recurrence in a wide range of tumors. Therefore, ERBB3 itself is the subject of increasing interest as a therapeutic target.[5] A recent study, exploiting genetically engineered mice, showed that ERBB3 is specifically expressed in a subset of GBM (~13%) originating from oligodendrocytic-progenitor cells and devoid of EGFR expression. This study provided the first evidence that ERBB3 inhibition can counteract tumor growth in this subset.[7]

By the use of the integrated human models, we shed light on the biological role of ERBB3 in GBM, identifying the requirements for GBM dependence on ERBB3 and for sensitivity to ERBB3 inhibition. In the NS cohort, we observed that marked ERBB3 overexpression is faithfully inherited from the human GBM and passed on to the experimental tumor (Figure 1). After ruling out the occurrence of *ERBB3* genetic alterations (such as amplification or mutations stabilizing expression), we found that the mechanism of heritable ERBB3 overexpression involves epigenetic inactivation of a specific microRNA, miR-205, known to be a major regulator of ERBB3 expression.[8] miR-205 inactivation hinges either on promoter hypermethylation or overexpression of lncRNA SNHG5, acting as a miR-205 sponge. In patients, we found that ERBB3 overexpression is associated with shortened survival of primary GBMs, and it is more frequent (up to 62%) in recurrent GBMs (www.cbioportal.org), suggesting that high ERBB3 activity may support tumor aggressiveness and therapeutic resistance. Consistently, in GSCs, we found that ERBB3 overexpression and activation sustains a boosted cellular metabolism, with increased extracellular acidification, oxidative phosphorylation and *de novo* fatty acid biosynthesis, which correlate with increased survival *in vitro* and tumorigenic potential *in vivo* (Figure 1). Surprisingly, we found that ERBB3 is overexpressed in the absence of its conventional EGFR family partners, so that it is

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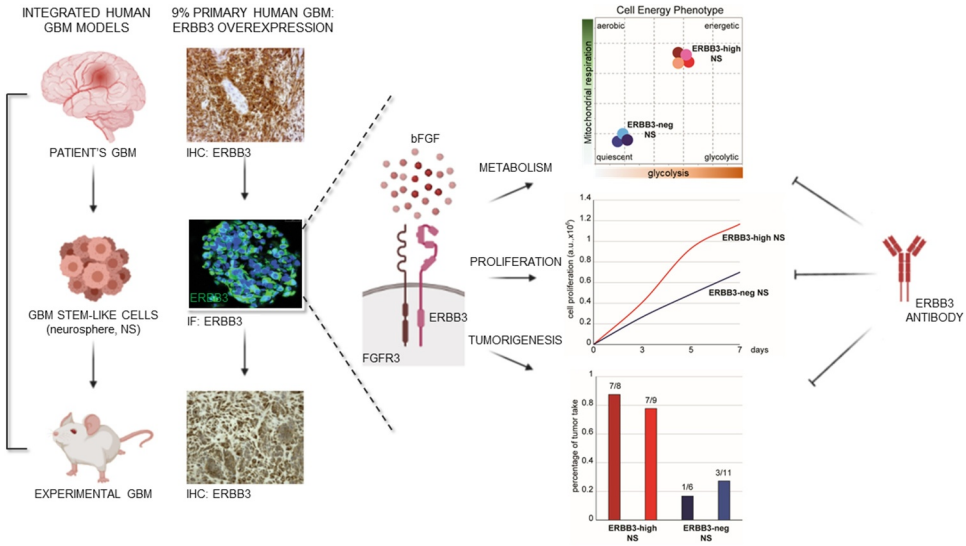

Figure 1. Overexpressed ERBB3 is passed-on from patient to experimental glioblastoma and enforces an aggressive phenotype. By investigating an integrated human glioblastoma (GBM) model including patient's tissues, their derived GBM stem-like cell cultures (neurospheres, NS) and experimental GBMs obtained by intracranial NS injection, we observed Erb-B2 receptor tyrosine kinase 3 (ERBB3) overexpression in 9% of matched samples. Overexpressed ERBB3 heterodimerizes with fibroblast growth factor receptor 3 (FGFR3) and is activated by basic fibroblast growth factor (bFGF), sustaining high metabolic and proliferation rates and *in vivo* tumorigenesis. These activities can be counteracted by specific anti-ERBB3 antibodies only in ERBB3 overexpressing models. IHC: immunohistochemistry; IF: immunofluorescence.

insensitive to EGFR family ligands, including Epidermal Growth Factor (EGF) and neuregulin. We found a still unreported interaction between ERBB3 and Fibroblast Growth Factor Receptor 3 (FGFR3), an essential regulator of neural stem cell biology. Indeed, overexpressed ERBB3 and FGFR3 heterodimerize in the presence of basic Fibroblast Growth Factor (bFGF), which is followed by ERBB3 phosphorylation, and powerful activation of the PI3K/AKT/mammalian target of rapamycin (MTOR) pathway. This pathway, linking ERBB3 overexpression to metabolic upregulation and cell survival, provides at the same time a potential Achille's heel. In ERBB3 overexpressing models (both NS and experimental tumors), ERBB3 inhibition *via* the specific antibody seribantumab (MM121)[9] switches the metabolic phenotype from highly energetic to quiescent. This results in proliferative blockade and apoptosis *in vitro*, and tumor growth arrest *in vivo* (Figure 1). Such therapeutic effects are not observed in cases expressing low ERBB3 levels (often EGFR-amplified GBMs), which conceivably rely on other molecular mechanisms for their growth and survival.

These findings highlight that sensitivity to ERBB3 inhibition tightly correlates with ERBB3 overexpression fixed by a mechanism (such as miR-205 epigenetic inactivation) inheritable throughout cell generations and likely selected during GBM evolution. Identification of GBM patients eligible for ERBB3 targeting would require a reliable biomarker. In our study we provide also evidence that, consistently with previous findings,[10] overexpressed ERBB3 can migrate into the cell nucleus. This observation offers a diagnostic opportunity and raises fascinating questions on still poorly explored ERBB3 pro-tumorigenic functions.

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Figure 1 has been created with BioRender.com.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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