Commentary

Shared Intelligence: A Patient-Derived, Deeply Characterized Glioblastoma Cell Line Resource

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The highly lethal brain cancer glioblastoma (GBM) is one of the most genomically well-characterized forms of cancer. Mutations in coding genes that occur at frequencies greater than 5% above background are likely to have already been identified (Lawrence et al., 2014), revealing a landscape of potentially actionable drug targets. Growth factor receptor amplification and mutations, including epidermal growth factor receptor (EGFR) alterations, PIK3CA mutations and PTEN deletion and mutation are especially common (Brennan et al., 2013). In all, growth factor receptor signaling is activated by copy number alterations and mutations in close to 90% of tumors sampled. To date, this information has yet to translate into new treatments or better outcomes for patients. Acting upon insights gained by the genomic roadmap will require a deeper understanding of how specific mutations cause tumors through reprogramming of signaling, metabolic, and epigenetic networks, particularly with regard to identifying therapeutic vulnerabilities (Cloughesy et al., 2014). Tumor models will play a central role in this effort. In this issue of EBioMedicine, Xie et al. provide an important, new, shared resource that directly addresses this critical need (Yuan et al., 2015).

Much of what we know about cancer, including GBM, has come through studying established tumor cell lines in culture. Adherent cancer cell lines in serum-containing culture, which are widely shared by the cancer research community, have been used to identify most of the oncogenes and tumor suppressors that we know are important in cancer. Further, studies in these established cell lines have yielded important insights into the behavior and function of tumor cells, including some aspects of the molecular determinants of response to treatments. The Cancer Cell Line Encyclopedia, a pioneering effort using such established cell lines, illustrates this point (Barrettina et al., 2012). Transgenes, siRNAs, shRNAs, and CRISPR constructs can readily be introduced into established cell lines, enabling exquisitely detailed gain and loss of function studies in an isogenic background. These types of relatively “reductionist” analyses in a simplified system remain exceptionally valuable, particularly when they are coupled to correlational studies in clinical samples, additional mechanistic studies in cell culture systems and in vivo models that may more accurately reflect the complex behavior of tumors in situ.

However, these established cell lines cultured in serum have a number of significant limitations. They are less heterogeneous than the tumors from which they are derived; they tend to lack the invasive growth pattern characteristic of GBMs when implanted into the brain; and some of the signature genetic alterations, including EGFR amplification and mutations such as EGFRvIII, are lost within a small number of in vitro passages. This may relate to the potential link between focal amplification of growth factor receptors in GBM and extrachromosomal DNA (Nathanson et al., 2014; Nikolaev et al., 2014), although this process is, as yet, incompletely understood. Serum-containing cultures also disfavor the putative glioma stem cell (GSC) population, which appears to play a potentially key role in the genesis, proliferation and drug resistance of GBM (Lathia et al., 2015). GSC lines have been developed and used extensively for studies in vitro and in vivo, but the relative shortage of GSC lines that are shared by the field, and the relative lack of high-resolution molecular and clinical data associated with these lines and the tumors from which they were derived, has limited their usefulness. A set of patient derived cell culture models that addresses these key concerns is needed.

Xie et al. have established a library of 48 patient derived cultures obtained from surgical resections of a representative set of patients. These cell lines, which are maintained in standard serum-free stem cell culture conditions, have been extensively characterized at the molecular level, revealing the mutations and DNA copy number variations that are present in the parent tumor and are characteristic of GBM in general. Transcriptional profiling of these lines, particularly with regard to the four main transcriptional subclasses (classical, mesenchymal, neural, and proneural), similarly reveals transcriptional programs that are shared with the tumor of origin and characteristic of GBMs in general. These cell lines also exhibit a GSC-like phenotype and form tumors in the brains of mice that recapitulate the histologic and molecular features of the GBMs from which they were derived.

Most importantly, the authors have taken their work a step further by committing to make this cell library, and the associated molecular and clinical data, an open resource that is fully available to the community through a supported online database. As such, the cell line models described in this manuscript substantially augment the current toolbox of patient derived xenograft models and existing GSC lines (Sarkaria...
et al., 2007; Joo et al., 2013). It is a gift to the community and ultimately to the patients.

The cancer research community is awash in data — genomic, transcriptomic, epigenomic, proteomic, and metabolic. The models have lagged behind. What are the “right” model systems? In what context should they be used? What are the strengths and limitations of such model systems? How can they be used as a resource for the field so that molecular insights can be reproducibly translated into new treatments and better outcomes for patients? The cancer research community is still figuring this out. Getting it right may be one of the key steps towards more effective translation of genomic insights into better therapies. Xie et al. have provided an important patient-derived, GSC-based cell line resource that augments the existing toolkit of established GBM cell lines, patient-derived xenografts and mouse genetic models. Each of these model systems has an important and proper place in the collective effort to turn scientific insight into more effective therapies for patients.

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