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RESEARCH HIGHLIGHT

The soft underbelly of tumor cells

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In a recent *Cell* paper, Kitambi and colleagues identify a small molecule (Vacquinol-1) that has beneficial effects on a glioblastoma multiforme mouse model by oral administration. In glioblastoma cells, Vacquinol-1 targets macropinocytosis, a cellular process that will not lead to cell death in normal cells.

Current treatments for glioblastoma multiforme (GBM) include surgical resection, when possible, with concomitant radiotherapy and chemotherapy. Yet GBM remains an essentially incurable disease with median survival of about one year. Kitambi and colleagues [1] report that a small molecule Vacquinol-1 can specifically induce human glioblastoma cell (GC) death, attenuate tumor progression and prolong survival in a GBM mouse model. Vacquinol-1 induces GC death by a catastrophic unconventional cell death pathway. Vacquinol-1 activates a form of clathrin-independent endocytosis — macropinocytosis. Massive macropinocytic vacuole accumulation leads to the rupture of GC cytoplasmic membrane and cell death. This work not only identifies a small molecule that may have suitable properties for GBM treatment, but also highlights an alternative strategy for drug development that targets cellular vulnerabilities that are not necessarily involved in the tumorigenic process.

GBM exhibits notable variability at the histopathological level. According to the 2007 Word Health Organization (WHO), three different glioblastomas are classified based on their histopathological features: small cell glioblastoma, glioblastoma with oligodendroglioma component, and glioneuronal tumor with neuropil-like islands [2]. It is also known that GBM arises by two pathogenically distinct routes, either from a preexisting low-grade astrocytoma (secondary GBM) or de novo in a fully malignant state (primary GBM) [3]. With the recent advances in genomics technology, the heterogeneity of GBM is also demonstrated at the molecular level. The Cancer Genome Atlas (TCGA) employed an unsupervised clustering of global transcriptional data in an attempt to define biologically meaningful distinctions with a sample set of more than 200 GBMs. This analysis designated four subclasses of GBM: proneural, neural, classical and mesenchymal. These tumors exhibit significant correlations to defined genomic and epigenetic abnormalities [4]. In the current *Cell* study, Vacquinol-1 identified from a compound screen, induces death of GCs but not mouse embryonic stem cells or human fibroblasts and does not appreciably affect zebrafish development. The specificity of this compound is further fortified by demonstrated activity in nine patient-derived GC cultures using stem cell culture conditions. Unfortunately, this study did not provide sufficient information for the GC cultures to assess whether they were widely representative of the human GBM subtypes. Importantly, oral administration of Vacquinol-1 substantially impairs disease progression and prolongs survival of mice transplanted with GCs.

Macropinocytosis is a form of endocytosis often seen in some immune cells, such as macrophages and dendritic cells. In other cell types, macropinocytosis is weak and requires growth factor stimulation [5]. Ernfors and colleagues show that GC cannot tolerate macropinocytosis activation. The massive accumulation of macropinocytic vacuoles caused by Vacquinol-1 leads to GC membrane rupture and death. However, activation of macropinocytosis does not always cause cancer cell death. For certain type of tumors, such as tumors expressing oncogenic Ras, macropinocytosis represents an important route of nutrient uptake. Pharmacological inhibition of macropinocytosis compromises the growth of Ras-transformed tumor xenografts [6]. The present work provides support for the authors' hypothesis that gain- and loss-of-function mutants in glioma could lead to unique cellular properties of GCs that are weak or absent in other cell types. Sensitivity to macropinocytosis is a unique cellular property of GCs, and thus this process can be exploited for development of new strategies for glioma therapy. Through an RNAi screen, the authors further found that the MAPKK, MKK4, provides key signaling for Vacquinol-1-induced macropinocytosis. MKK4 belongs to the Ser/Thr protein kinase family and is activated by environmental stress and inflammatory signals [7]. Upon activation, MKK4 phosphorylates downstream MAP kinases, such as JNK1/2 and p38, but not Erk1/2 [8]. MKK4 mRNA is expressed in most adult tissues with high expression in central nervous system and liver during embryonic development [9]. MAP2K4 mutations have been reported in some tumor cells, including pancreas, ovary, prostate and breast cancers, and its role in suppression of metastasis has been proposed in prostate and ovarian

cancers [7]. However, there also exists evidence for oncogenic function of MKK4. For example, MKK4-deleted cells showed reduced tumorigenesis and lung metastasis compared to the parental MKK4-intact pancreatic cancer cells [10]. These pro- and anti-tumorigenic functions of MKK4 in different models are not yet fully reconciled. Nevertheless, in the current *Cell* study, the identification of MKK4 could provide another target for glioma drug development.

The identification of core "tumor driver" signaling pathways in tumor formation has steered drug development strategies from more empirical cell-based assays to major efforts to develop targeted therapies. However, the present study highlights the continued utility of empirical cell-based screens that adopt a better understanding of the biological principles of cancer cells. Kitambi and colleagues performed a screen with NCI diversity set II compound library. This library is composed of 1 364 compounds that have been selected based on their availability in the NCI repository and structural diversity from the original 140 000 small molecules, and now replaced by NCI diversity set IV. Thus, taking advantage of this collection, the authors performed screening with primary tumor cells cultured from human GBM patients rather than from established cancer cell lines.

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