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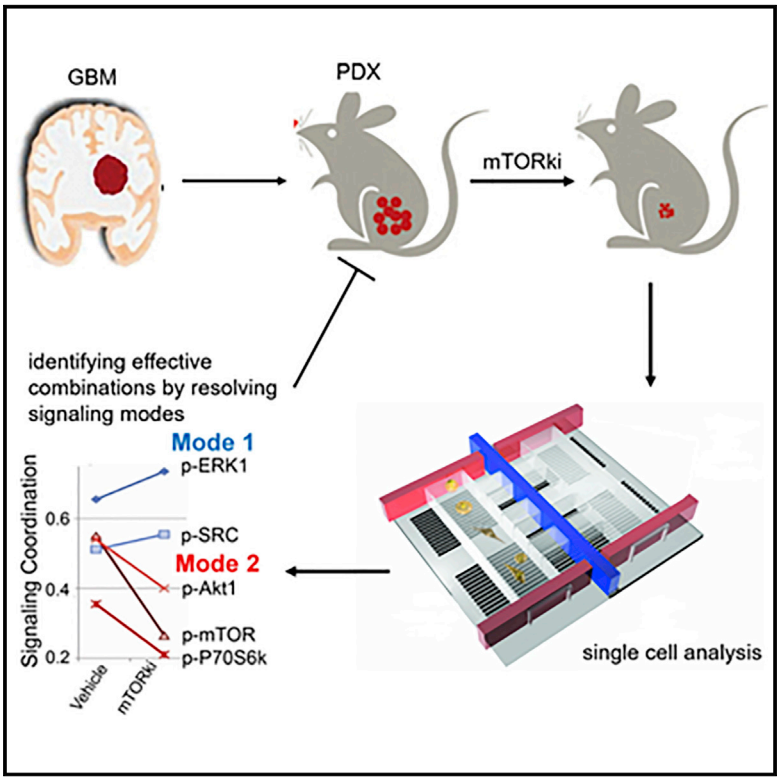
Single-Cell Phosphoproteomics Resolves Adaptive Signaling Dynamics and Informs Targeted Combination Therapy in Glioblastoma

Graphical Abstract



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In Brief

Wei et al. utilize single-cell phosphoproteomic analysis of patient-derived glioblastoma models to identify shifts in signaling coordination following short-term treatment with kinase inhibitors, which facilitates the design of combination therapy approaches with reduced resistance and improved efficacy.

Highlights

- Sequencing excludes the selection of an mTORki-resistant genotype in a GBM model
- Heterogeneous signaling networks rapidly adapt to mTORki to drive resistance
- Resistance-promoting signaling is observed a priori by single-cell analysis
- Network analyses point to therapy combinations for long-term disease suppression

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Single-Cell Phosphoproteomics Resolves Adaptive Signaling Dynamics and Informs Targeted Combination Therapy in Glioblastoma

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SUMMARY

Intratumoral heterogeneity of signaling networks may contribute to targeted cancer therapy resistance, including in the highly lethal brain cancer glioblastoma (GBM). We performed single-cell phosphoproteomics on a patient-derived in vivo GBM model of mTOR kinase inhibitor resistance and coupled it to an analytical approach for detecting changes in signaling coordination. Alterations in the protein signaling coordination were resolved as early as 2.5 days after treatment, anticipating drug resistance long before it was clinically manifest. Combination therapies were identified that resulted in complete and sustained tumor suppression in vivo. This approach may identify actionable alterations in signal coordination that underlie adaptive resistance, which can be suppressed through combination drug therapy, including non-obvious drug combinations.

INTRODUCTION

Glioblastoma (GBM), one of the most lethal human cancers, is a paradigmatic example of intratumoral heterogeneity. The Cancer Genome Atlas (TCGA) has revealed that prevalent GBM mutations and copy-number variations (CNVs) cluster along a small set of druggable signaling pathways, including (1) receptor tyrosine kinase (RTK)/RAS/PI3K signaling, (2) p53 signaling, and (3) Rb signaling (Brennan et al., 2013). However, clinical trials with targeted monotherapies against these mutations or their downstream effectors have yet to favorably affect patient outcomes, as tumors rapidly acquire resistance (Cloughesy and Mischel, 2011; Nathanson et al., 2014). Intratumoral molecular heterogeneity may play a critical role in cancer drug resistance, and new technologies that facilitate resolving such heterogeneity, including single-cell RNA, DNA, and even protein analyses (Irish et al., 2004; Kalisky et al., 2011; Shi et al., 2012; Wu et al., 2014) are becoming increasingly available. Mining such information to

Significance

Genomic analyses of GBM tumors have revealed a core set of mutations that reside along druggable pathways, but drugs targeted to those pathways have only marginally improved patient outcomes, with the rapid development of drug resistance being almost universal. Using genomics and single-cell phosphoproteomics analyses of a human-derived in vivo GBM model of mTORki resistance, we show that drug resistance can proceed via a non-genetic (adaptive) mechanism that is activated within days of drugging. The measured adaptive response points to combination therapies that are tested in vivo and shown to halt tumor growth. This single-cell analytic approach appears to provide clinically actionable insights into designing combination therapy strategies for more effectively treating GBM patients.