Stony Brook University
The Graduate School

Doctoral Defense Announcement

Abstract

The Emergence of Drug Tolerance in Cancer Cell Populations

By

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Drug resistance continues to be a major obstacle to curing cancer. Recent work has shown that resistance can evolve from a subpopulation of cancer cells that initially survive drug treatment and form a pool of slowly cycling, drug-tolerant cells. Several studies have pinpointed activation of a specific bypass pathway that appears to provide the critical therapeutic target for preventing drug tolerance. Currently, efforts against these targets have not yielded clinical success, and the question of how to block drug-tolerant cells remains unanswered.

To address this, we used proteomic and genomic methods to probe the full scope of changes that accompany the development of drug tolerance to EGFR inhibitors in *EGFR*-mutant lung adenocarcinoma cells and to BRAF inhibitors in *BRAF*-mutant melanoma cells. We found that there are numerous alternate mitogenic signaling pathways that become activated in both cases, including YAP, STAT3, IGF, and phospholipase C (PLC)/protein kinase C (PKC) pathways. We used single-cell RNA-sequencing to determine that these signaling pathways are simultaneously upregulated in individual cells adapting to drug. We also uncovered several programs associated with cell survival and slow growth, that appear enriched in drug-treated cells. To demonstrate the utility of disrupting these mechanisms, we used various inhibitors in combination with targeted therapies to block the emergence of drug-tolerant cells. Unexpectedly, genetic validation studies did not always mirror the results obtained with pharmacological inhibitors.

These results offer a completely different framework for understanding how drug-tolerant cells are able to survive and slowly cycle in the presence of targeted therapies. Additionally, we offer evidence that suggests effective therapeutic strategies will need to take multiple alternative mitogenic pathways into account, rather than focusing on one specific pathway. Finally, our genetic studies suggest that some co-treatment strategies may reduce the number of drug-tolerant cells via off-target ROS-induced apoptosis, rather than through the drug's intended mechanism.

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(*If an outside member of the community would like to attend the defense, please contact Martha.Furie@stonybrookd.edu)