Sequential Application of Anticancer Drugs Enhances Cell Death by Rewiring Apoptotic Signaling Networks

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DOI 10.1016/j.cell.2012.03.031

SUMMARY

Crosstalk and complexity within signaling pathways and their perturbation by oncogenes limit component-by-component approaches to understanding human disease. Network analysis of how normal and oncogenic signaling can be rewired by drugs may provide opportunities to target tumors with high specificity and efficacy. Using targeted inhibition of oncogenic signaling pathways, combined with DNA-damaging chemotherapy, we report that time-staggered EGFR inhibition, but not simultaneous coadministration, dramatically sensitizes

cell death (Harper and Elledge, 2007). The DDR is highly interconnected with other progrowth and prodeath signaling networks, which function together to control cell fate in a nonlinear fashion due to multiple levels of feedback and crosstalk. Thus, it is difficult to predict a priori how multiple, often conflicting signals will be processed by the cell, particularly by malignant cells in which regulatory networks often exist in atypical forms. Predicting the efficacy of treatment and the optimal design of combination therapy will require a detailed understanding of how the DDR and other molecular signals are integrated and processed, how processing is altered by genetic perturbations commonly found in tumors, and how networks can be "rewired" using drugs individually and in combination (Sachs et al., 2005).