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# Metronomic Chemotherapy Modulates Clonal Interactions to Prevent Drug Resistance in Non-Small Cell Lung Cancer

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## Abstract

Despite recent advances in deciphering cancer drug resistance mechanisms, relapse is a widely observed phenomenon in advanced cancers, mainly due to intratumor clonal heterogeneity. How tumor clones progress and impact each other remains elusive. In this study, we developed 2D and 3D non-small cell lung cancer co-culture systems and defined a phenomenological mathematical model to better understand clone dynamics. Our results demonstrated that the drug-sensitive clones inhibit the proliferation of the drug-resistant ones under untreated conditions. Model predictions and their experimental *in vitro* and *in vivo* validations indicated that a metronomic schedule leads to a better regulation of tumor cell heterogeneity over time than a maximum-tolerated dose schedule, while achieving control of tumor progression. We finally showed that drug-sensitive and -resistant clones exhibited different metabolic statuses that could be involved in controlling the intratumor heterogeneity dynamics. Our data suggested that the glycolytic activity of drug-sensitive clones could play a major role in inhibiting the drug-resistant clone proliferation. Altogether, these computational and experimental approaches provide foundations for using metronomic therapy to control drug-sensitive and -resistant clone balance and highlight the potential of targeting cell metabolism to manage intratumor heterogeneity.

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