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TARGETED THERAPIES

New rational design approach to optimize combination therapy strategies

Macmillan

A new approach to identify the most-effective combinations of existing chemotherapies has shown that drug regimens can be designed to maximize tumour cell death while minimizing tumour subpopulation outgrowth. "Our mathematical models could very effectively predict outcome and tumour composition in an *in vivo* model of B-cell lymphoma," explains Michael Hemann, lead author of the study. "We can predict both therapeutic outcome and the trajectory of tumour subclones in response to combination therapy."

Tumours undergo branched clonal evolution—cycles of clonal expansion, diversification and selection. Additional genetic changes accumulate during cancer progression, which contribute to tumour heterogeneity. This spatial and temporal heterogeneity of cancers poses a substantial challenge to the rational design of therapeutic regimens. "Recent work has suggested that emergence of resistant clones in tumours treated with front-line chemotherapy might not be accompanied by clear resistance-causing mutations," explains Hemann. He continues, "this curious finding suggests that clonal selection itself may promote the emergence of drug resistance and that the maintenance of tumour heterogeneity might represent a desirable clinical outcome."

Building on their previous algorithms that predict tumour response to therapy, the researchers now provide an approach to select drug combinations that effectively target heterogeneous tumours, and they validated the predictions *in vitro* and *in vivo*. "We made use of a short hairpin RNA (shRNA) signature approach developed by Justin Pritchard that allows us to visualize drug action as a pattern of shRNA-mediated sensitivity or resistance," says Hemann. "In other words, it provided us with a mathematical approach to look at drug combination." This information in turn was used to predict optimal combination chemotherapeutic regimens for heterogeneous tumours (in this case, of up to three subpopulations of cells).

To validate their predictions, the team used *in vitro* fluorescence-based competition assays to track the enrichment, or depletion, of the subpopulations. In addition, a murine lymphoma model was used to show that they could predict the combination treatments that minimize the emergence of tumour subpopulations and prolong overall survival.

Importantly, the investigators found that knowledge of the predominant subpopulation is often insufficient for identifying the optimal drug combination. Furthermore, sometimes the optimal drug combination does not include the drugs that would most effectively treat any particular subpopulation, according to expression of the target for the particular chosen therapy.

This research provides the first steps in designing targeted anticancer combination therapies that take intratumour heterogeneity into account, and highlights some of the approaches and principles that will be important for finding optimal combination therapies in the case of intratumour diversity of complex tumours. "In the near future, we plan to apply this same approach to human tumours sequenced before and after therapy to see if we could predict the effect of therapy on the clonal composition of these tumors," comments Hemann. "Subsequently, we could apply a similar minimization approach to see if the maintenance of heterogeneity in these tumours correlates with the delayed emergence of chemoresistance."

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Original article Zhao, B. *et al*. Addressing genetic tumor heterogeneity through computationally predictive combination therapy. *Cancer Discov.* doi:10.1158/2159-8290.CD-13-0465