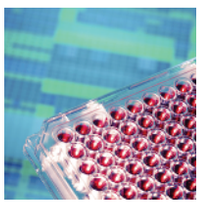
Drug Response

Major finding: Dynamic BH3 profiling predicts therapeutic response and identifies optimal treatments.

Approach: Dynamic BH3 profiling measures changes in early death signaling in response to drug treatment.

Impact: This functional approach is a potential rapid-response tool for personalized cancer therapy.

INITIATION OF DEATH SIGNALING PREDICTS CYTOTOXIC RESPONSE TO THERAPY



Biomarkers that predict patient response to anticancer therapy have yet to be identified in most cases. Efforts to identify biomarkers have largely focused on tumor genotype and lack measurement of functional responses to perturbations in cancer cells. Montero and colleagues developed a rapid-response platform in which isolated cancer cells were treated with a panel of chemotherapeutic agents and assessed for early changes in mitochondrial priming, or apoptotic sensitivity, in response to treatment. This technique, named Dynamic BH3 Profiling (DBP), effectively predicted response to therapy in both cell lines and clinical samples. As a proof of principle, non–small cell lung cancer and breast cancer cell lines with varying therapeutic resistances were treated with a panel of tyrosine kinase inhibitors. By 16 hours post-treatment, an increase in BH3 peptide–induced mitochondrial depolarization was detected in sensitive cell lines, indicative of an increase in priming, and significantly correlated with increased apoptosis at 72 hours post-treatment, supporting the hypothesis that early induction of death signaling predicts the cytotoxic response to drug days later. In addition, DBP was capable of identifying the optimal kinase inhibitor that induced the greatest cytotoxicity in both hematologic cancer and solid tumor cell lines *in vitro* as well as in a mouse melanoma allograft model *in vivo*, demonstrating its power across multiple tumor lines and a wide range of inhibitors, including drug combinations. Furthermore, DBP of primary patient cells distinguished clinical sensitivity and resistance to imatinib in patients with chronic myelogenous leukemia and predicted progression-free survival in patients with ovarian adenocarcinoma treated with carboplatin, indicating that short-term analysis of clinical samples via DBP may stratify patients most likely to respond to therapy. Overall, these data establish DBP as a useful tool to rapidly predict patient response to therapy and suggest that DBP may be exploited as a biomarker to guide individual patient treatment. ■

Montero J, Sarosiek KA, DeAngelo JD, Maertens O, Ryan J, Ercan D, et al. Drug-induced death signaling strategy rapidly predicts cancer response to chemotherapy. Cell 2015;160:977–89.

Immune Evasion

Major finding: Shedding of a natural killer (NK) cell activating receptor ligand by tumor cells promotes tumor rejection.

Concept: Soluble ligands can prevent ligands on host cell membranes from desensitizing NK cell receptors.

Impact: Treatment with soluble NK cell receptor ligands may be an effective way to stimulate immunosurveillance.

SHED NATURAL KILLER CELL LIGANDS CAN BE ACTIVATING

Natural killer (NK) cells are innate immune cells that play a key role in cancer immunosurveillance by recognizing and eliminating tumor cells. One way tumor cells may evade NK cells is through excreting or shedding ligands of NKG2D, an activating receptor on the surface of NK cells. Although the function of soluble NKG2D ligands is not entirely clear, they are thought to downregulate NKG2D expression on NK cell surfaces by promoting receptor endocytosis and to induce defects in NK cell activation due to persistent engagement and resulting desensitization of NKG2D. Deng and colleagues transduced murine tumor cells that normally do not shed NKG2D ligands with the NKG2D ligand MULT1 and made the unexpected observation that these tumor cells were rejected by syngeneic mice in an NK cell–dependent manner. Tumor cells engineered to release MULT1 or injection of recombinant MULT1 into tumors stimulated NK functional activity, suggesting that soluble MULT1 induces tumor rejection by activating NK cells. However, unlike membrane-bound MULT1, which crosslinks and activates NKG2D while simultaneously downregulating its expression on the cell surface, soluble MULT1 did not directly activate NKG2D and did upregulate its cell surface expression. This observation led the authors to hypothesize that other NKG2D ligands expressed on non-tumor host cell membranes persistently engage NKG2D on NK cells, leading to NKG2D downmodulation and NK cell desensitization, whereas soluble MULT1 blocks these interactions to increase NK cell responsiveness. Indeed, tumor-associated myeloid cells displayed NKG2D ligands such as RAE-1 that downregulated NKG2D cell surface expression on NK cells and suppressed functional NK responses to tumor cells, whereas recombinant MULT1 blocked the binding of RAE-1 to NKG2D. In addition to establishing that soluble NK cell ligands are not always inhibitory, these findings raise the possibility that activating soluble ligands could be used to augment antitumor immune responses. ■

Deng W, Gowen BG, Zhang L, Wang L, Lau S, Iannello A, et al. A shed NKG2D ligand that promotes natural killer cell activation and tumor rejection. Science 2015 Mar 5 [Epub ahead of print].

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