Los Alamos simulation tests innovative cancer treatment approach

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More than 30 percent of human cancers have mutations in a small, specific group of genes, but attempts to design drugs specifically for these cancers have been unsuccessful.

Known as *Ras* genes, named for the specific protein family called **Ra**t **S**arcoma, for which the genes code, the Ras-regulated signal pathways control such processes as actin cytoskeletal integrity, cell proliferation, cell differentiation, cell adhesion, apoptosis and cell migration.

There are drugs available that target a similar protein, Raf, from **R**apidly **A**ccelerated **F**ibrosarcoma, which is in the same signaling pathway as Ras. Unfortunately these drugs (called RAF inhibitors) are ineffective in *Ras*-mutant tumors, and even *RAF*-mutant tumors quickly develop resistance to RAF inhibitors.

The international collaboration's aim was to identify combinations of RAF inhibitors that would be able to effectively treat both *Ras*- and *RAF*-mutant tumors.

They built a mathematical model of the RAS signaling pathway using BioNetGen, a rule-based modeling language that was developed at LANL. Using this model, they could simulate treatment of diverse cell types with different types of RAF inhibitors.

The simulations predicted that specific combinations of inhibitors would have a synergistic effect, where the drug combination is stronger than expected (e.g., 1+1 = 3). The best pairing of drugs, which combined a Type II and a Type I 1/2 RAF inhibitor, was synergistic in cell lines with RAS mutation, RAF mutation, or both.

"We tested the model predictions in experiments with melanoma cell lines, and confirmed the the combinations were synergistic," said Keesha Erickson, a Los Alamos researcher on the project. The Type II + Type I 1/2 drug combinations were able to markedly inhibit signaling through the pathway and dramatically reduce cancer cell growth.

These findings are interesting, she said, because a typical drug combination strategy is to use two drugs with different targets to impair tumor growth. "Here, we are actually recommending to hit the same target (RAF), but with two different drugs. This works because different types of RAF inhibitor recognize different conformations of RAF. The Type II RAF inhibitor binds strongly to RAF in one conformation, while the Type I 1/2 drug binds RAF when it is in a different conformation. Together, these drugs can better inhibit RAF than with either single drug alone, since more possible conformations are recognized by the pair of drugs."

“The next step is to test these drug combinations in xenograft experiments. Potential collaborations at the National Cancer Institute could be an important step before these combinations could be evaluated in clinical trials, and hopefully eventually help a large proportion of cancer patients,” Erickson said.

The Paper: Dissecting RAF Inhibitor Resistance by Structure-based Modeling Reveals Ways to Overcome Oncogenic RAS Signaling, Cell Systems, DOI: https://doi.org/10.1016/j.cels.2018.06.002

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