Tailoring an anti-cancer drug for optimal tumor cell killing

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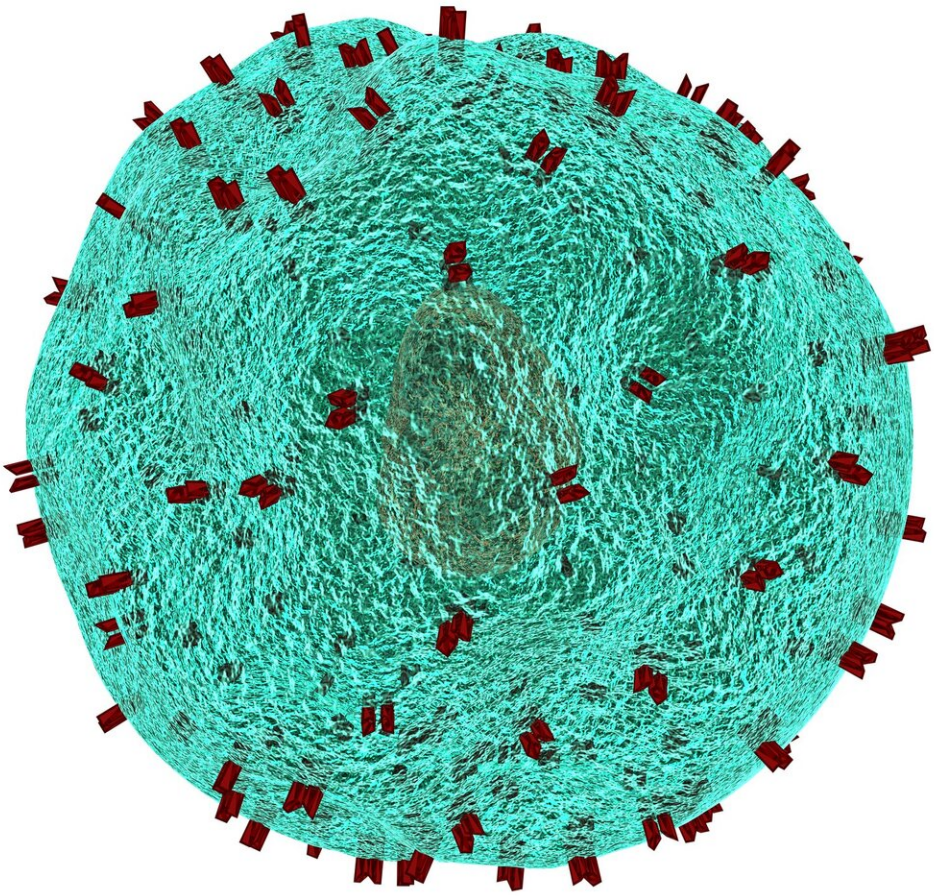

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In a study published this week in *Science*, Université de Montreal researchers report key structural and biochemical differences among a class of anti-cancer drugs known as PARP inhibitors. These distinguishing differences were linked to differing capacities of PARP inhibitors to kill cancer cells. The research resolves a long-standing and perplexing quandary over differences between the effectiveness of PARP inhibitors used in cancer clinics.

Moreover, the researchers used their structural and biochemical insights to introduce modifications to an existing PARP inhibitor, and thereby increased its capacity to kill cancer cells. "The principle behind this tailoring of PARP inhibitor molecules also has applications beyond cancer therapy, for example in other indications such as cardiovascular disease and inflammation, where PARP inhibitor use is also being evaluated," says John Pascal, a senior author on the study.

PARP inhibitors target the enzyme PARP-1. PARP-1 is a primary responder to breaks in the structure of DNA, a chronic form of genome damage that is under constant surveillance and repair. PARP-1 has two major activities: binding to DNA breaks, and creating a molecule known as poly(ADP-ribose). PARP inhibitors all bind to the same region of PARP-1 and prevent PARP-1 from making poly(ADP-ribose), and this activity interferes with PARP-1 contribution to the repair of DNA damage. The loss of PARP-1 contribution to DNA repair is acceptable in healthy cells; however, cancer cells with re-configured DNA repair mechanisms, such as those deficient in the repair protein BRCA1 or BRCA2, have become dependent on PARP-1 and are selectively killed by PARP inhibitors.

Prior to the study in *Science*, it was unclear whether PARP inhibitors could also affect the second activity of PARP-1, binding to damaged DNA. The PARP inhibitors that are most effective in the clinic tend to "trap" PARP-1 on DNA, which is thought to prevent cancer cells from dividing. The authors of the study asked whether there could be a structural aspect of PARP inhibitors that increases PARP-1 interaction with DNA. "We were quite surprised to find that some PARP inhibitors actually decreased PARP-1 interaction with damaged DNA," says Marie-France Langelier, a lead author of the study. One of these PARP inhibitors, Veliparib, decreased PARP-1 binding to DNA and is poor at killing cancer cells compared to other PARP inhibitors. Veliparib thus seems to work against the PARP-1 "trapping" process by weakening PARP-1 interaction with DNA. This result provided a key clue to the puzzle: By comparing the structure of Veliparib to clinical PARP inhibitors that do trap PARP-1 on DNA, the authors were able to identify differences in the structures that could account for the ability of the inhibitors to trap versus weaken interactions with DNA.

Using Veliparib as a starting molecule, the researchers engineered a new PARP inhibitor that did have the capacity to increase PARP-1 interaction with DNA, and this new PARP inhibitor showed greater cancer cell killing relative to Veliparib. "It was rewarding to see that the biochemical and structural studies were consistent and predictive of the behaviors that I observed in the cell killing assays" continued Langelier.

The results of this study also open up new avenues to designing PARP inhibitors for treating other diseases. While PARP inhibitors used in cancer treatment are selected for their ability to kill cancer cells, there are others used to treat inflammation or cardiovascular disease where the goal is to preserve cells and guard against tissue damage associated with hyper activation of PARP-1. Thus, the ability to tailor PARP inhibitors to reduce PARP-1 trapping on DNA could be important in these applications. The study provides the design principles for tailoring

PARP inhibitors to specific applications. "PARP inhibitors have generated excitement in the medical community and they have established new prospects for treating disease. We are thrilled that our structural and biochemical approach to understanding PARP-1 can guide the continued development of PARP inhibitors," says John Pascal.

More information: "Structural basis for allosteric PARP-1 retention on DNA breaks" *Science* (2020). science.sciencemag.org/cgi/doi … 1126/science.aax6367

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