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How chemotherapy becomes more effective

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Researchers from the University of Zurich have found a cellular brake that protects cancer cells from chemotherapy -- and they demonstrate which medication can be used to render it inoperative. Their study published in the journal *Natural Structural and Molecular Biology* provides the molecular basis for promising therapeutic advances.

Although many cancer drugs have already been in use for decades, their mode of action is still unknown. The new research results now challenge a mechanism of action that was previously proposed for a group of drugs and supported with experiments: the Topoisomerase I-inhibitor Camptothecin (Top1 inhibitor for short) and its derivatives used in chemotherapy, Topotecan and Irinotecan.

Problem: emergency cellular brake restricts effectiveness

For a long time, the toxicity of the top1-inhibitors was attributed to discontinuities in the cancer cells' DNA that inevitably caused breaks in the chromosomes during the duplication of the DNA. The team headed by Professor Massimo Lopes at the University of Zurich's Institute of Molecular Cancer Research has now identified a mechanism with which cancer cells protect themselves against damage caused by Top1 inhibitions: Using electron microscopy, the researchers were able to demonstrate that Top1 inhibitors can cause the replication forks that develop during the duplication of the DNA to be restructured. "Reversed" replication forks, or "chicken-foot" structures as they are also known, are formed. This remodeling of the replication forks

provides the cancer cells with the time they need to repair the lesion in the DNA and thus prevent disparately cytotoxic chromosomal breakage.

"Until now, the assumed mechanism of action of Top1 inhibitors was comparable to a train hurtling towards an obstacle without brakes that inevitably ends up derailing," explains Massimo Lopes, commenting on the results. "What we have now discovered is the emergency brake, which the cells activate themselves to protect themselves from the inhibitor." Arnab Ray-Chaudhuri, who made a considerable contribution to the study, draws the following conclusion: "Thanks to the discovery of this mechanism, we now understand why chemotherapy does not always work as expected with these drugs."

The existence of such DNA structures was hypothesized many years ago, but it has only just been confirmed in human cells by Lopes's group. These chicken-foot structures are even surprisingly common with clinically relevant doses of Top1 inhibitors.

Solution: render emergency brake inoperative

The new observations reveal an interesting coincidence: In pulling the emergency brake, a family of enzymes that recently attracted a great deal of interest as a potential target for new cancer therapies is involved in the restructuring: the poly-ADP-ribose polymerases, or PARPS for short. After all, PARP inhibitors increase the sensitivity of cancer cells to different drugs that harm the DNA, including Top1 inhibitors. The new study reveals why: PARP inhibition hinders the reversal of the replication forks and increases the number of chromosomal breaks caused by Top1 inhibitors. Massimo Lopes and his team thus provide a clear molecular basis for the clinical observations described and pave the way for promising therapeutic advances.

Massimo Lopes's team is currently investigating whether the same or a

similar mechanism is activated by other classes of chemotherapeutics and which cellular factors are involved in this molecular "emergency brake". The aim is to identify tumors in which this mechanism is not active or inhibit the mechanism pharmacologically to improve the efficacy of chemotherapy.

More information: A. Ray Chaudhuri, Y. Hashimoto, R. Herrador, K.J. Neelsen, D. Fachinetti, R. Bermejo, A. Cocito, V. Costanzo and M. Lopes. Toposiomerase I poisoning results in PARP-mediated replication fork reversal. *Nature Structural and Molecular Biology*. 4 March, 2012. Doi: 10.1038/nsmb.2258