Two-pronged attack on DNA repair could kill drug-resistant cancers

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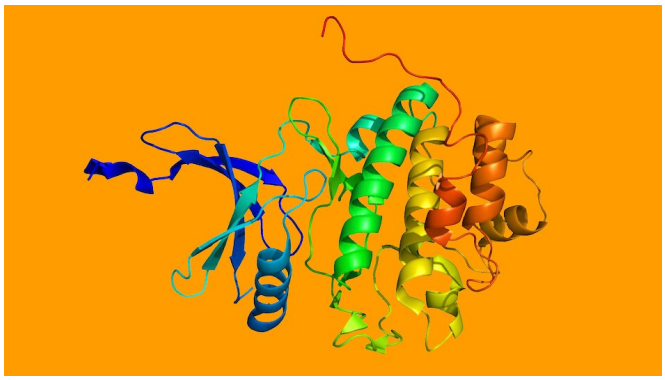

Protein structure of checkpoint kinase 1 (via PyMOL). Credit: Emw via Wikimedia Commons, CC BY-SA 3.0

Launching a two-pronged attack on cancer's ability to safeguard its DNA could offer an effective new way of treating the disease, a new study reports.

Scientists have found that small molecules that stop cancer cells from copying their DNA can boost the effectiveness of drugs called CHK1 inhibitors, which are designed to stop cells from patching up their genomes.

CHK1 inhibitors weaken the ability of cancer cells to cope with DNA damage. The researchers discovered that when another set of genes involved in accurately copying genetic material are also blocked, this leads to catastrophic levels of DNA damage and 'replicative stress' - causing cancer cells to die.

They hope that a combination strategy that attacks DNA repair by inhibiting CHK1 and blocking accurate DNA replication at the same time could be effective against lung, bowel and other cancers—including ones that are resistant to current treatments.

Scientists at The Institute of Cancer Research, London, and the University of Kent treated lung and bowel cancer cells in the lab with a new experimental drug called SRA737, which blocks CHK1, and screened thousands of genes for targets that could be inhibited to increase cancer cell killing.

Using this approach, the researchers discovered that inhibiting a family of proteins known as B-family DNA polymerases—which are involved in the accurate replication of DNA—was highly effective in combination of SRA737.

Their study is published in *Cancer Research*, a journal of the American Association for Cancer Research. It was funded by Wellcome, with additional support from other organisations, including The Institute of Cancer Research (ICR) itself.

The researchers found that when they targeted the B-family DNA polymerases, cancer cells became more vulnerable to treatment with SRA737. Combined treatment with SRA737 and an experimental inhibitor of B-family DNA polymerases called aphidicolin stripped cancer cells of their ability to cope with DNA damage, and was more effective at killing them in eight of the nine cancer cell lines tested.

The researchers at the ICR—a charity and research institute—and the University of Kent believe that blocking both CHK1 and B-family DNA polymerases using a future combination of drugs could potentially be an effective cancer treatment.

This is an example of the kind of approach the ICR plans to take within its pioneering Centre for Cancer Drug Discovery, which aims to combat the central challenge of cancer evolution and drug resistance. The ICR has less than £10 million left to raise of the £75 million cost to create and equip the new building.

The researchers also found that low levels of the B-family DNA polymerases within tumours could be used as an indicator to pick out patients who may be more likely to respond to treatment with a CHK1 inhibitor when used on its own. More research will be needed, but this could bring CHK1 inhibitors a step closer to clinical use.

Combination approaches that use CHK1 inhibitors alongside other drugs, like the chemotherapy drug gemcitabine, have already shown promise in previous studies—including early clinical trials in cancers of the anus and genitals.

The new findings suggest the combination of SRA737 alongside an inhibitor of B-family DNA polymerases such as aphidicolin is also promising. However, aphidicolin is no longer being developed as it was found to be toxic.

Instead, the next step will be to discover suitable B-family DNA polymerase drug candidates, so the benefit of combination treatment with CHK1 inhibitors like SRA737 can be investigated in animals.

Study co-leader Professor Paul Workman, Chief Executive of The Institute of Cancer Research, London, said:

"Our new study establishes the basis for a potentially exciting new approach to treatment involving a two-pronged attack on cancer. We found that doubling up on drugs that target the systems for repairing DNA could be effective even against cancers that do not respond to single-drug treatment.

"Our findings also provide us with a way of picking out which patients are most likely to benefit from existing CHK1 inhibitors like SRA737—a highly innovative drug discovered at the ICR and currently in clinical development.

"At the ICR, we believe that combinations of targeted drugs will be critical as we aim to overcome the major challenge of cancer evolution and drug resistance—just as they have been in other diseases such as HIV."

Study co-leader Professor Michelle Garrett, previously a Team Leader at The Institute of Cancer Research, London, and currently Professor of Cancer Therapeutics at the University of Kent, said:

"Our study shows the potential of targeting DNA replication for adding to the effect of an existing drug that blocks a system that helps respond to DNA damage.

"It's exciting too that detecting tumours with low levels of B-family DNA polymerases could be used to identify patients most likely to respond to a CHK1 inhibitor, presumably because of natural weaknesses in DNA repair within these cancers.

"The next step is to develop new drug candidates that could be used to target B-family DNA polymerases in combination with the CHK1 inhibitor SRA737, as we have shown that this could open up a potential new therapeutic approach."

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