PARG inhibitors: tipping the scales with a new experimental drug

March 17 2017

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When cancer cells divide they often make mistakes which can alter their DNA. While this can give cancer cells an upper hand, it can also be their downfall.

Some DNA mistakes change molecules inside the cells in such a way that they offer an advantage for the tumour cells over healthy cells,

allowing them to grow uncontrollably. But other mistakes are just too damaging for the cells to handle, causing them to die.

It's like a set of scales that the cells must balance to keep growing.

To help them do this, cancer cells can also use DNA repair mechanisms to fix potentially fatal faults that develop over time.

But even though these DNA repair kits can keep the scales balanced, cancer cells are more reliant on these repair molecules to survive than healthy cells.

This makes certain cancer cells particularly vulnerable to drugs that switch off DNA repair molecules and which can upset the cancer cell's balance.

This strategy has recently seen several promising drugs, collectively called PARP inhibitors, now being used to treat some women with ovarian cancer.

But they don't work for everyone.

That's why Dr Donald Ogilvie, and his team based at Drug Discovery Unit, at Cancer Research UK's Manchester Institute, have turned their focus on a different molecule: PARG.

And their recent study, published in the journal *ACS Chemical Biology*, might lead to a new way to target how cancer cells repair DNA, and maybe do it better.

Sabotaging DNA repair

Dr Allan Jordan, Head of Chemistry in the Manchester Institute Drug

Discovery Unit (CRUKMI DDU), devotes his time to studying potential new drugs. And he believes it's the close proximity between the institute's labs and the neighbouring Christie Hospital that helps speed up the process.

Experimental drugs, in preparation at the CRUK Manchester Institute Drug Discovery Unit . Credit: Ben McMahon

"Our team wants to translate the fantastic biology that goes on in the institute's labs into medicines for patients, like those at the hospital next door. We see 40,000 patients there a year, and only around half will beat their disease. Our job is to find something for the other half."

Their ambition was to target DNA repair molecules in a way that would help some of these patients, and the first step was to understand why PARP inhibitors don't work for everyone.

One reason for this is that there are 17 different members of the PARP family. And like most families, although they share similarities, each molecular sibling is slightly different from the other.

This gives the PARP family an advantage over the drugs that have been developed to switch them off. Drugs are designed very specifically according to the exact shape of the molecules they target. So most PARP drugs only switch off 2 or 3 members of the family.

This means that there's a chance that other family members will take their place and compensate for the loss, bypassing the drug's effects.

But PARP molecules are just one of many DNA repair tools that a cancer cell can deploy. So are there alternatives that could be targeted with new drugs?

This is where the DDU team turned its attention to PARP's molecular cousin, PARG.

A single target

PARG is also involved in repairing cells' DNA. But, unlike the sprawling PARP family, there's only one of this type of molecule.

And this, according to Jordan, makes it an excellent target for drugs.

"The advantage of going after PARG is that there is only one member of its family. So when you inhibit PARG, you may create a more effective roadblock in DNA repair," he explains.

PARG is part of the same DNA repair toolkit as PARP. As PARP repairs DNA, it constructs a molecular scaffolding frame which attracts other essential components of DNA repair.

Experimental drugs, in preparation at the CRUK Manchester Institute Drug Discovery Unit . Credit: Ben McMahon

But for the repair to take place, this scaffold needs to be carefully and methodically, disassembled. And this is where PARG comes in – disassembling that scaffolding, piece by piece in a safe, ordered manner.

So disabling PARG might tip the DNA damage scales towards being lethal for the cancer cells.

Tipping the scales

Discussing this idea with UK-based pharmaceutical company AstraZeneca, researchers found the teams there had already started looking for experimental drugs to block PARG, among 1.4 million potential experimental drugs.

For Jordan, this meant the next steps weren't going to be easy.

"The number of molecules that AstraZeneca had already looked at told us we were facing quite a challenge. But it was a challenge we were willing to take on," he says.

Sifting through all the potential drugs AstraZeneca had tested, they found that one in particular was very good at stopping PARG from doing its job. In fact, the team's research has now found that one of its optimised PARG experimental drugs is even better at killing certain cancer cells growing in the lab than PARP inhibitors.

But while they have experimental drugs that look promising, there's still a way to go.

"This is not going to lead to a new treatment for patients overnight. First we need to understand the biology, how the experimental drug works and how to find which patients it works best for, before we can get it into clinical trials and patients," says Jordan.

"However, we believe this is a really exciting time for PARG."

"It's fantastic that Cancer Research UK is so involved in this work, just as it was for PARP inhibitors that are now approved medicines and benefiting patients. It could lead to the development of PARG inhibitors as a new type of treatment for cancer."

More information: Dominic I. James et al. First-in-Class Chemical Probes against Poly(ADP-ribose) Glycohydrolase (PARG) Inhibit DNA Repair with Differential Pharmacology to Olaparib, *ACS Chemical Biology* (2016). DOI: 10.1021/acschembio.6b00609

Provided by Cancer Research UK