

Using DNA repair processes to target cancer

February 27 2015, by Kat Arney



Unfortunately, our DNA isn't as easy to repair as this paper model. Credit: Alex Bateman

Every day our DNA is under attack.

The brunt of this assault comes from the basic processes of life, which cause DNA-damaging chemicals to be released inside [cells](#). But there are also external forces at work: carcinogens in tobacco smoke, ultraviolet rays from the sun and sunbeds, radiation from natural or man-made sources and much, much more.

Whatever the cause, this damage must be repaired in order for cells to carry on functioning properly.

On the whole, our cells are exceptionally good at this and, for most of our lives, things usually go according to plan.

But if mistakes are made, bad things can happen – bad things like cancer.

Poorly repaired DNA damage can cause changes in important genes that control cell growth, meaning that cells can start multiplying out of control and form tumours.

Over the years, our scientists and others around the world have unpicked the biological 'toolkits' our cells use to repair their damaged DNA. And it turns out that rather than being a strength, problems with DNA repair can be a critical weakness in cancer cells, leading to an exciting new approach for tackling the disease.

Earlier this month we spotted two papers in the journal *Nature* that provide a new insight into cancer's DNA repair mechanisms, which could be exploited to develop new treatments.

Two wrongs can make a right

The key concept to understand here is synthetic lethality, and it works like this:

Cells have several molecular toolkits to repair different types of genetic damage. And some are more accurate than others. If parts of these 'good' toolkits are missing or broken (as is often the case in cancer cells) the cells have to resort to using less effective 'backup' methods.

Targeting these alternative systems with drugs leaves cancer cells with no way of repairing DNA damage, so they die.

As we've written about before, this idea forms the basis of an entirely new class of drugs for treating cancer, known as PARP inhibitors. PARP – or poly-ADP ribose polymerase, to give it its full name – is a protein found in all our cells, and forms part of this backup repair system. It is particularly critical in cancer cells with faults in genes called BRCA1 or BRCA2, which play an important role in gluing together breaks in DNA. Errors in these genes are relatively common in several types of cancer, notably breast, ovarian and prostate cancers that run in families.

Using PARP inhibitor drugs in cancer cells that already lack BRCA1 or 2 knocks out their back-up repair system, leaving them fatally damaged.

Cancer Research UK-funded scientists played a crucial role in the early development of PARP inhibitors, and the first of them, olaparib (Lynparza), has now been licensed for use within the EU for women with a certain type of ovarian cancer.

But, as we mentioned earlier, our cells have evolved many different DNA repair mechanisms to cope with the insults that life throws at them. Over recent years the hunt has been on to find out whether other repair processes might be exploitable in the same way as PARP.

The two Nature papers highlight a new target for this kind of approach – a protein known as polymerase Q, or PolQ.

PolQ to the rescue

The research teams behind both papers were focusing on a particular type of DNA damage where the double helix is completely snapped in two – something known as a double-strand break. It's the most toxic of

all types of DNA damage in cells, and they have a number of ways to repair these breaks.

One method, homologous recombination ensures that any neighbouring bits of broken DNA are glued together again. Importantly, these ends can't be 'clean' breaks – there needs to be a little bit of overlapping DNA sequence on each side of the damage (a bit like frayed ends of a broken rope) so the cell knows that it's gluing together the right bits.

Cells 'prefer' to fix double strand breaks through homologous recombination, as it's more accurate.

But sometimes – for example, if the molecules involved are missing or faulty, or if there isn't any overlapping DNA sequence – the more accurate method isn't possible and they have to use an alternative.

In these circumstances, cells switch to a process called non-homologous end-joining. Rather than ensuring that the broken bits of DNA actually belong together, this repair toolkit just glues together any stray ends it finds. That's fine if the two ends spanning a break have stayed in the same place. But it's less good if there is lots of damage. In this situation, random DNA sequences can get stuck together, causing genetic chaos in the cell.

So in one of the Nature studies, the researchers were trying to find out how cells cope when they can't accurately repair their DNA using their preferred, homologous recombination toolkit.

The scientists studied cells grown in the lab that had been experimentally manipulated so they were forced to use an alternative repair pathway. When they looked closely at the repairs that had been made, they saw that short sequences of DNA had been inserted – a classic hallmark of the work of a type of molecule called a DNA polymerase.

DNA polymerases are responsible for creating new stretches of DNA, either to fix damage or when a cell copies all its genetic material in order to divide into two cells. When the US team looked carefully at their modified cells, they discovered that a polymerase called PolQ was responsible for the repairs.

In the other paper – from a trans-Atlantic collaboration that includes prize-winning scientist Simon Boulton from our London Research Institute – the researchers came at the problem from a different angle.

In this case they noticed that certain ovarian tumours had unusually high levels of PolQ, particularly those that also had a faulty homologous recombination toolkit – for example, a missing BRCA1 gene.

And when they got rid of PolQ in cells carrying these faults, the cells died.

Together, both studies show us that PolQ is playing a role in the back-up repair system that kicks into action if cells can't fix DNA breaks in their preferred way. This suggests that designing drugs that target PolQ could be effective in treating cancers lacking parts of the main DNA repair kit – BRCA1 or the related BRCA2, for example.

Sloppy copiers

To find out more about the new research, and how it might point towards new cancer therapies, we spoke to Professor Steve Jackson at the Gurdon Institute in Cambridge. He and his team carried out a lot of the early work on PARP inhibitors and, unsurprisingly, he's a big fan of the synthetic lethality approach.

"We know that there are a range of polymerases, and that some of them have been linked to DNA repair," he told us. "It turns out that some of

them are not very accurate and what they do – they're sloppy copiers. I remember we used to have debates at conferences about whose polymerase was the most inaccurate! But they're like that for a reason. It allows them to cope with damaged DNA that normal polymerases will turn their nose up at."

Although PolQ has been known about for a few years, it was only previously shown to be possibly involved in DNA repair in fruit flies. So finding that it plays an important role in human cancers is a big step forward.

"These new papers provide a potential new therapeutic target for certain cancers that are relying on [homologous recombination](#), such as some breast and ovarian cancers," Steve tells us, "but only time will tell what the true impact of this work is."

If it's broke, break it some more

At the moment, the researchers have used a lab technique to knock out PolQ in [cancer cells](#), which wouldn't be suitable for using in patients. So would it be tricky to develop a drug to block PolQ?

"As drug targets go, this polymerase has a lot going for it. I think the challenge now – and I think it's an exciting one – is whether drugs can be developed against it. There are chemicals that can do it, but you'd want to block this polymerase and not anything else."

Steve feels that PolQ is an attractive target for drug developers to set their sights on, and with focused effort it should be possible to develop compounds that selectively attack it.

But will it work?

"We'll only know from cell-based studies and then follow on studies how good a target this is. At this stage it's difficult to know how strong the effect would be compared to what you might get with PARP inhibitors, and that will only be demonstrated when somebody's got a potential drug that is able to switch off PolQ."

For now, these are just ideas and results from lab experiments. But thanks to the work of Steve, Simon and other researchers in our labs and around the world, they're coming closer to being a reality for cancer patients.

And that can't come soon enough.

More information: Mateos-Gomez P.A. et al (2015). "Mammalian polymerase θ promotes alternative NHEJ and suppresses recombination," *Nature*, 518 (7538) 254-257. [DOI: 10.1038/nature14157](https://doi.org/10.1038/nature14157)

Ceccaldi R. et al (2015). "Homologous-recombination-deficient tumours are dependent on Pol θ -mediated repair," *Nature*, 518 (7538) 258-262. [DOI: 10.1038/nature14184](https://doi.org/10.1038/nature14184)

Provided by Cancer Research UK

Citation: Using DNA repair processes to target cancer (2015, February 27) retrieved 19 April 2024 from <https://medicalxpress.com/news/2015-02-dna-cancer.html>

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