THERAPY

Addicted to repair

DOI:

10.1038/nrc2155

URLs

PARP1

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&md=Retrieve&dopt=full_report&list_uids=142

BRCA1

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&md=Retrieve&dopt=full_report&list_uids=672

BRCA2

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&md=Retrieve&dopt=full_report&list_uids=675

FANCG

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&md=Retrieve&dopt=full_report&list_uids=2189

ATM

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&md=Retrieve&dopt=full_report&list_uids=472

FANCD2

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&md=Retrieve&dopt=full_report&list_uids=2177

FANCC

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&md=Retrieve&dopt=full_report&list_uids=2176

Pancreatic cancer

<http://www.cancer.gov/cancertopics/types/pancreatic>

Fanconi anaemia

<http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=227650>

The rationale for developing anticancer drugs that target DNA damage response (DDR) pathways has been strengthened by the encouraging results from using inhibitors of poly(ADP-ribose) polymerase 1 (PARP1), a member of the base excision repair (BER) pathway, to selectively kill *BRCA1*- or *BRCA2*-deficient tumour cells, which are incapable of activating homologous recombination DNA repair pathways. Such strategies rely on identifying DDR pathways that are crucial to the maintenance of genomic stability in cells that are already compromised for at least one DDR pathway. This prompted Alan D'Andrea and colleagues to identify DDR pathways that compensate for the loss of the **Fanconi anaemia** (FA) DDR pathway.

Defects in members of the FA DDR pathway have an established association with inherited predisposition to cancer, in the form of FA itself or *BRCA2* heterozygosity, and are increasingly associated with sporadic cancers. The authors used a small interfering RNA (siRNA) library, which targets 230 DDR genes, to identify genes that confer survival

in FA complementation group G (**FANCG**) cells, which are defective in FA pathway activity. They confirmed that the BER pathway is important for the survival of these cells; however, they also identified three members of the ataxia-telangiectasia mutated (**ATM**)-dependent DDR pathway, including ATM itself. Indeed, ATM was active at a low level in FA cells. Surprisingly, they showed that *Atm*^{-/-}; *Fancg*^{-/-} mice are not viable, demonstrating that ATM-dependent and FA DDR pathways are essential for survival and function in parallel, despite previous data showing that ATM phosphorylates **FANCD2**, a component of the FA DDR pathway.

The authors showed that DNA breaks increased in FANCG cells that had been treated with ATM siRNA, indicating that ATM is required for the repair of spontaneous DNA breaks that occur in the absence of the FA pathway. Therefore, governed by the same rationale as the application of PARP1 inhibitors, D'Andrea and colleagues used the ATM-specific competitive inhibitor KU55933 to

investigate whether FA pathway-deficient cells were more sensitive to ATM inhibition.

They found that the drug significantly increased apoptosis in FA cell lines, and clonogenic survival assays showed that FA complementation group C (**FANCC**; also defective in the FA pathway) cells were more sensitive to KU55933 compared with controls. Moreover, they showed that FANCC- and FANCG-deficient human **pancreatic cancer** cell lines were sensitive to KU55933.

D'Andrea and colleagues have added more weight to the rationale of targeting DDR pathways to increase the selectivity of tumour cell killing, especially given that the loss of DDR pathways could be an early stage in tumorigenesis that generates genomic instability.

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ORIGINAL RESEARCH PAPER Kennedy, R. D. et al. Fanconi anemia pathway-deficient tumour cells are hypersensitive to inhibition of ataxia telangiectasia mutated. *J. Clin. Invest.* 12 April 2007 (doi: 10.1172/JCI31245)

FURTHER READING Turner N. et al. Hallmarks of 'BRCAness' in sporadic cancers. *Nature Rev. Cancer.* 4, 814–819 (2004)