Credit: Richard Drury

MILESTONE 4

A licence to kill

Synthetic lethality, a term coined by Theodosius Dobzhansky in 1946, arises when co-occurring mutations in two genes kill cells, whereas mutation of either gene alone does not and may elicit a milder phenotype. This phenomenon was first described by Calvin Bridges in 1922 in genetic experiments in *Drosophila melanogaster*. Mechanisms underlying synthetic lethality are now known to include genetic and non-genetic redundancies, buffers and adaptation.

A few decades later, the concept of synthetic lethality was applied to cancer research, ultimately leading to the approval of new therapies. Rapidly dividing cells had long been known to be susceptible to drug-induced DNA damage, suggesting that DNA-repair inhibitors might selectively kill cancer cells. By the 1980s, inhibitors of the DNA-repair poly(ADP)–ribose polymerase (PARP) enzymes had been shown to kill cancer cells more efficiently in concert with DNA-damaging agents than as single agents. Then, in a seminal 1997 article, Leland Hartwell, Stephen Friend and colleagues suggested that synthetic-lethality relationships could lead to new anticancer drug targets, and genetics might therefore offer a rational approach to drug discovery. Because genetic and drug screens were then largely limited to model organisms, the researchers used a *Saccharomyces cerevisiae* screen, focusing on defects in DNA-repair and cell-cycle genes. Indeed, some chemotherapeutic drugs selectively killed cells with specific genetic mutations.

> “The results strikingly revealed a large therapeutic window (or index) both in vitro and in mice.”

Building on these findings, two landmark studies in 2005 by Alan Ashworth’s group in collaboration with KuDOS Pharmaceuticals Ltd. and the groups of Thomas Helleday and Nicola Curtin demonstrated that human cancer cells with mutations in the DNA-repair tumour-suppressor genes *BRCA1* and *BRCA2* are selectively sensitive to PARP inhibitors. Loss of the base-excision-repair enzyme PARP1 increases DNA lesions, such as collapsed replication forks, which can normally be repaired through homologous recombination (HR). Therefore, the teams reasoned that defects in BRCA1 or BRCA2, which participate in HR, might be synthetically lethal with the loss of PARP1 or PARP inhibition. Indeed, cells with deletion of *B*RCA1 or BRCA2 (or other HR genes) were viable but died after PARP-inhibitor treatment. The results strikingly revealed a large therapeutic window (or index) both in vitro and in mice. The findings were notable because people with *BRCA1* or *BRCA2* germline mutations are predisposed to breast, ovarian and prostate cancer, and the tumours that develop exhibit loss of BRCA function and impaired HR. Subsequent observations from the groups of Alan Ashworth and Toshiyasu Taniguchi showed that resistance to PARP inhibitors or platinum (which also targets HR) can arise due to unexpected secondary function-restoring alterations in *BRCA2* providing further evidence of a synthetic-lethal relationship.

As a direct result of this work, in 2014, the PARP inhibitor olaparib became the first targeted therapy for the treatment of patients with ovarian cancer with germline *BRCA1/2* mutations to be approved by the European Medicines Agency (EMA) and US Food and Drug Administration (FDA). Olaparib and three other PARP inhibitors have since been approved for several other malignancies, some with loss of BRCA1/2 function (breast, pancreatic and prostate cancer).

Beyond associations with specific genetic mutations, drugs may synergize, such that treatment with one cancer drug exposes a vulnerability to a second drug. In 2012, René Bernards and colleagues studied why melanoma cells with the activating V600E alteration in the kinase BRAF are sensitive to BRAF inhibitors, but colorectal cancer cells with the same mutation are not. In a synthetic-lethality screen, BRAF inhibition in colorectal cancer cells exposed a sensitivity to the concomitant loss or inhibition of the receptor tyrosine kinase EGFR, both in vitro and in vivo. This synergy arose from rapid feedback activation of EGFR signalling after BRAF-inhibitor treatment. In contrast, melanoma cells express little EGFR; therefore, BRAF inhibitors did not stimulate EGFR activation. These findings led to the 2020 EMA and FDA approval of combination treatment with the BRAF inhibitor encorafenib and the EGFR-targeting antibody cetuximab for *BRAF*-mutant metastatic colorectal cancers.

Examples of cancer-specific synthetic-lethal relationships in mammalian cells and strategies to systematically discover and exploit synthetic-lethal interactions for cancer therapy were discussed in an influential 2005 review by William Kaelin, and many still hold true. The application of synthetic lethality has rapidly advanced, and sophisticated, high-throughput genetic and drug screens, and more recently CRISPR–Cas9 technology are often used. Drugs have been approved for more indications, and many more clinical trials based on the principles of synthetic lethality are underway. Current areas of exploration include cell-intrinsic mechanisms, such as the BRCA–PARP and BRAF–EGFR interactions, and vulnerabilities mediated by the tumour microenvironment, such as combinations of targeted drugs with immunotherapies.

Barbara Marte, *Nature*

ORIGINAL ARTICLES Bryant, H. E. et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. *Nature*. **434**, 913–917 (2005) | Farmer, H. et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. *Nature*. **434**, 917–921 (2005) | Prahallad, A. et al. Unresponsiveness of colon cancer to BRAF(V600E) inhibition through feedback activation of EGFR. *Nature*. **483**, 100–103 (2012).
FURTHER READING Please visit the online article for a full list of further reading.