CLINICAL IMPLICATIONS OF BASIC RESEARCH

Elizabeth G. Phimister, Ph.D., *Editor*

Signatures of DNA-Repair Deficiencies in Breast Cancer

Nicholas C. Turner, Ph.D.

A woman who receives a diagnosis of breast cancer today is half as likely to die from cancer as she was three decades ago, in part owing to treatments that target expression of the estrogen receptor and the cell-surface receptor HER2 (human epidermal growth factor receptor 2) in subtypes of cancers. Although the expression of the estrogen receptor and the expression of HER2 are relatively common, there are many other potential targets for cancer treatment, each of which is very rare, occurring in only a few percent of patients with cancer. How can we identify enough patients with these rare breast cancers in order to conduct clinical trials of new treatments? One solution is to establish which rare cancers share common features, thus allowing them to be combined for clinical trials that target the group as a whole. Davies et al.[1] and Polak et al.[2] have recently described a basis for this approach, focusing on identifying cancers with a common defect in DNA repair.

Most cancers are caused by the accumulation of somatic, cancer-specific mutations in DNA. Various processes, including environmental factors such as smoking and ultraviolet light, the inactivation of DNA-repair mechanisms, and other, as yet unidentified, processes, lead to the acquisition of mutations. Each different mutational process results in a particular pattern of mutations, representing a signature, in the DNA of the cancer.[3] The inactivation of a specific type of DNA repair called homologous recombination is relatively frequent in breast cancer, causing elevated rates of mutations as well as chromosomal alterations. Most of these mutations have no effect or a negligible effect on the function of the cell under normal conditions; they are called "passenger" mutations, although a few "driver" mutations alter protein function, resulting in uncontrolled growth, invasion, and metastasis. The hereditary breast-cancer genes *BRCA1* and *BRCA2* are required for homologous recombination DNA repair, and multiple other defects in the same DNA-repair pathway have now been identified in breast cancer (Fig. 1).

Mutations that are caused by defective homologous recombination DNA repair occur in a very specific pattern, or signature (Fig. 2).[3] The two research groups found that this mutation signature in cancer DNA is a robust way of identifying which breast cancers have a defect in homologous recombination DNA repair, regardless of the underlying cause. Similar results have also been reported for other types of cancer.[4] Defective homologous recombination DNA repair can be targeted by specific drugs, such as inhibitors of

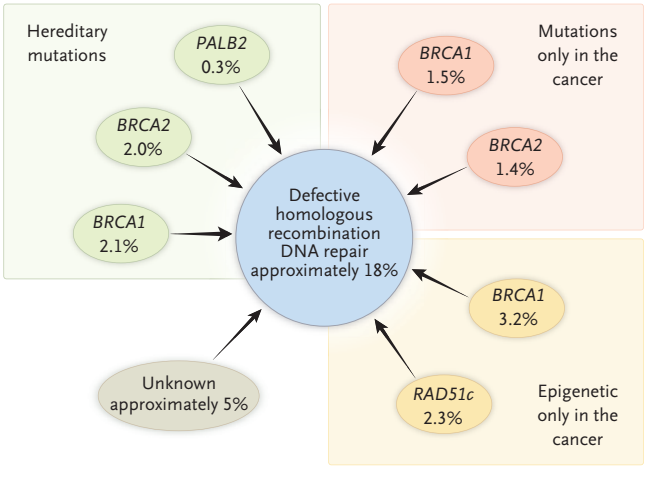

Figure 1. Paths to Defective Homologous Recombination DNA Repair in Breast Cancer.

Each individual mutation or epigenetic aberration occurs at low frequency.[1,2] However, when these mutations are summed together, defective homologous recombination DNA repair is a common feature of breast cancer.

poly-(adenosine diphosphate–ribose) polymerase (PARP), that cause specific types of DNA damage that can be effectively repaired only by homologous recombination–based DNA repair; cancer cells that are deficient in homologous recombination DNA repair cannot tolerate this additional damage and so die (Fig. 2). These approaches have already been shown to be effective in the treatment of hereditary *BRCA1* and *BRCA2* breast cancer in the clinic.[5]

Mutational signatures are permanently ingrained in the DNA of cancer cells, but tumors evolve over time and in response to treatment. The assessment of mutational signatures cannot distinguish whether the underlying defect in DNA repair is currently active or may have been reversed during tumor evolution, especially in patients in whom resistance to treatment develops. Although recent data suggest that the reversal of the DNA-repair defects could occur relatively frequently in patients with metastatic breast cancer, it is unknown to what extent this resistance mechanism may undermine this new approach to precision medicine for patients with early-stage breast cancer.

Polak et al. also showed how this characteristic mutation signature may help to solve a different clinical challenge. Germline genetic testing to identify hereditary breast cancer frequently identifies variants of unknown significance in the germline DNA sequence: variants that are nearly always benign but occasionally pathogenic. Having such a variant may cause anxiety, and some patients may even elect to have unnecessary double mastectomies. Current methods are imperfect in ascribing pathogenic status to very rare variants. Polak et al. found that the genomic signature that is caused by defective DNA repair in the cancer, together with the loss of heterozygosity of the variant (all the "normal" alleles of *BRCA* are lost in the cancer), may help to ascribe pathogenicity to a germline variant that would otherwise be categorized as one of unknown significance. This aspect of the study, although intriguing, is best described as a proof of principle; further extensive work is needed before the signature could be used to define pathogenic variants in the clinic.

There are at least 30 other mutation signatures reflecting different mutational processes, many of which have no currently known cause; there is a pressing need to identify the underlying causes,[6] which may in turn reveal new treatment and prevention approaches. Davies et al. and Polak et al. used tests that are used by research laboratories to detect the mutation signatures. It is now important to develop clinical-grade assays that can be widely and reproducibly used to identify these signatures. Clinical trials

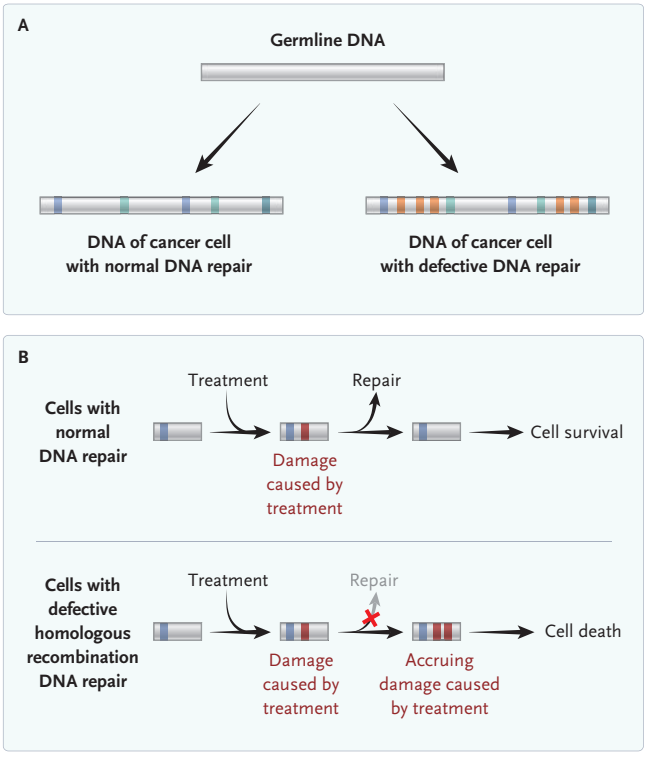

Figure 2. Making Sense of Signatures to Treat Breast Cancer.

All cancers acquire mutations in their DNA that are not present in the germline DNA of noncancer cells (Panel A). Cancers with defective homologous recombination DNA repair develop mutations with a characteristic pattern or signature (orange) that occurs in specific sequence contexts. There are more than 30 signatures, reflecting different processes that trigger changes in DNA (green and blue, indicating mutations in other signatures). The identification of cancers with an underlying defect in homologous recombination DNA repair may, in turn, identify patients who could benefit from specific DNA-damaging treatments (Panel B). Cancer cells with defective homologous recombination DNA repair are unable to repair DNA damage (red) that is caused by specific treatments, such as carboplatin chemotherapy and new targeted drugs such as inhibitors of poly-(adenosine diphosphate–ribose) polymerase (PARP). Damaged DNA accumulates in the cancer cell, ultimately leading to cancer-cell death. The high rate of mutations in these cancers may also make the cancer vulnerable to new immunotherapy approaches that aim to stimulate cytotoxic T cells to attack the cancer.

that classify patients according to cancer-mutation signature will be some of the first to move away from trials that classify patients according to a single cancer gene. Although language would suggest that genotype and phenotype are distinct entities, we can now envisage the cancer genome as having a phenotype, which will be a focus of a new generation of precision-medicine trials.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

From the Breast Cancer Now Research Centre, Institute of Cancer Research, and the Breast Unit, Royal Marsden Hospital, London.

1. Davies H, Glodzik D, Morganella S, et al. HRDetect is a predictor of BRCA1 and BRCA2 deficiency based on mutational signatures. Nat Med 2017;23:517-25.
2. Polak P, Kim J, Braunstein LZ, et al. A mutational signature reveals alterations underlying deficient homologous recombination repair in breast cancer. Nat Genet 2017;49:1476-86.
3. Alexandrov LB, Nik-Zainal S, Wedge DC, et al. Signatures of mutational processes in human cancer. Nature 2013;500:415-21.
4. Riaz N, Blecua P, Lim RS, et al. Pan-cancer analysis of bi-allelic alterations in homologous recombination DNA repair genes. Nat Commun 2017;8:857.
5. Robson M, Im S-A, Senkus E, et al. Olaparib for metastatic breast cancer in patients with a germline *BRCA* mutation. N Engl J Med 2017;377:523-33.
6. Drost J, van Boxtel R, Blokzijl F, et al. Use of CRISPR-modified human stem cell organoids to study the origin of mutational signatures in cancer. Science 2017;358:234-8.

DOI: 10.1056/NEJMcibr1710161