Uncovering a new principle in chemotherapy resistance in breast cancer

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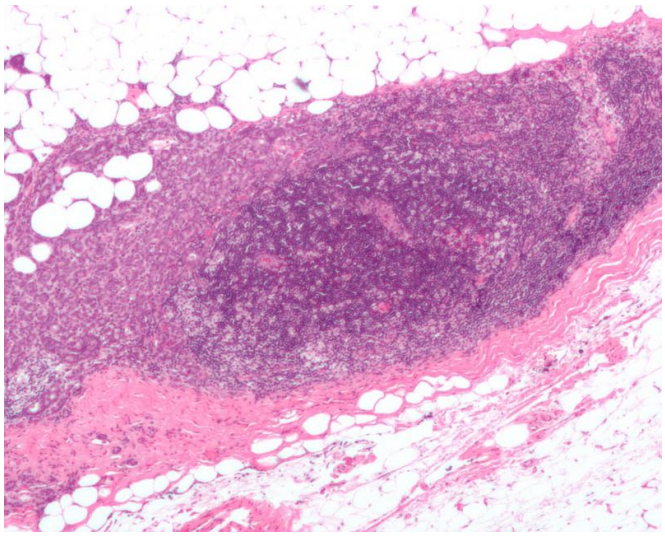

Micrograph showing a lymph node invaded by ductal breast carcinoma, with extension of the tumour beyond the lymph node. Credit: Nephron/Wikipedia

A laboratory study has revealed an entirely unexpected process for acquiring drug resistance that bypasses the need to re-establish DNA damage repair in breast cancers that have mutant BRCA1 or BRCA2 genes. The findings, reported by Andre Nussenzweig, Ph.D., and Shyam Sharan, Ph.D., at the National Cancer Institute (NCI), part of the National Institutes of Health, and colleagues, appeared July 21, 2016, in *Nature*.

In normal cells, the proteins BRCA1 and BRCA2 act as DNA damage sensors, surveyors, and responders. They help perform complex functions that facilitate the repair of damaged DNA. Individuals who inherit certain mutations in either the *BRCA1* or *BRCA2* gene have defective DNA repair and an increased risk of developing breast, ovarian, and other cancers. Specifically, mutations in *BRCA1* and *BRCA2* account for 20 percent to 25 percent of hereditary breast cancers and 5 percent to 10 percent of all breast cancers. The reduced ability to repair breaks in DNA in cells with a *BRCA1* or *BRCA2* mutation makes the cells sensitive to DNA damaging drugs. However, breast cancers eventually acquire resistance to these drugs. One documented mechanism for developing chemoresistance in such tumors is through the restoration of accurate DNA repair pathways that mend DNA breaks caused by chemotherapy.

Nussenzweig's laboratory has spent the past decade trying to understand the cellular mechanisms that regulate DNA repair in normal and pathogenic states. "It is the intricate mechanisms that tumor cells evolve to bypass the need for accurate DNA repair that form the foundation of our study," said Nussenzweig. "A deeper knowledge of the processes that drive drug resistance in -mutant tumors will lead to novel therapeutic approaches that target tumor-specific vulnerabilities."

In this study, the researchers linked the protection and stabilization of DNA replication forks as a major contributory mechanism to drug resistance in BRCA1/2-mutant breast and ovarian cancers. Replication is a cellular process that produces two indistinguishable DNA copies from a single DNA molecule. This DNA-copying process is an essential step in cellular division and occurs at defined locations called replication forks.

The movement of a replication fork as it migrates along a DNA molecule can be disrupted by the presence of a diverse group of DNA structures and proteins, collectively and loosely referred to as replication fork barriers. This interruption of replication fork migration results in what is called a stalled fork. Upon replication fork stalling, the BRCA1 and BRCA2 proteins are called upon to protect the newly synthesized strands of DNA. If these proteins are absent, the replication fork is destabilized and the newly synthesized DNA is degraded, which increases genomic instability and

increases sensitivity to DNA-damaging drugs.

The investigators were able to identify other proteins, such as PTIP, CHD4 and PARP1, that actively promote replication fork destabilization through the recruitment of enzymes that degrade newly synthesized DNA. The absence of these proteins protected the DNA at replication forks and remarkably reversed the drug sensitivity of both *BRCA1*- and *BRCA2*-mutant cells, making them chemoresistant. These studies also highlighted the complex ways by which tumor cells can evade chemotherapeutic interventions and acquire drug resistance, since disrupting the activity of multiple proteins led to the same end point of replication fork protection. These results are of particular relevance in the clinical setting, where expression of these proteins appears to be an indicator of how patients with *BRCA1*- and *BRCA2*-mutant cancers will respond to chemotherapeutic treatment with DNA-damaging agents.

All together, these results underscore the importance of replication fork barriers to genomic instability and drug sensitivity in the context of *BRCA1/2* mutations. The results also suggest that the cellular levels of these proteins could be used as a prognostic factor in acquired resistance in *BRCA1/2*-mutant cancers.

"Our work is starting to not only refine, but also redefine, the current dogma in the field, which states that restoring DNA repair pathways are the only means by which *BRCA1/2*-mutant cells can become chemoresistant," concluded Nussenzweig.

More information: Arnab Ray Chaudhuri et al. Replication fork stability confers chemoresistance in BRCA-deficient cells, *Nature* (2016). DOI: 10.1038/nature18325

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