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# Synthetic Lethality between Cancer Driver Genes and DNA Repair Pathways in Triple-negative Breast Cancer

**Greefeld Warn***

*Department of Urology, University of California, San Francisco, USA*

## Introduction

Triple-Negative Breast Cancer (TNBC) is a clinically aggressive and molecularly heterogeneous subtype of breast cancer characterized by the absence of estrogen receptor, progesterone receptor, and HER2 amplification. Due to the lack of targeted therapies, TNBC is typically treated with chemotherapy, which is often associated with high relapse rates and poor prognosis. Recent advances in cancer genomics have revealed that TNBC harbors frequent mutations in a distinct set of cancer driver genes, including TP53, BRCA1, MYC, and PIK3CA. A promising therapeutic strategy for TNBC lies in exploiting synthetic lethality, a concept where the simultaneous perturbation of two genes results in cell death, whereas alteration of either gene alone is tolerable. Targeting DNA repair pathways that interact synthetically with driver gene mutations may provide selective vulnerabilities unique to TNBC cells, offering new avenues for treatment [1].

## Description

In this study, we systematically investigate synthetic lethal interactions between recurrent cancer driver gene mutations and DNA repair pathway components in TNBC. Utilizing a combination of large-scale genomic datasets from The Cancer Genome Atlas (TCGA) and functional screening data from CRISPR-Cas9 and RNA interference platforms, we identify gene pairs whose co-inactivation selectively impairs TNBC cell viability. Our approach integrates mutation profiling with DNA repair gene expression, pathway activity scores, and cell line dependency data to uncover functionally relevant interactions. Notably, we find that BRCA1-deficient TNBC tumors display heightened sensitivity to the loss of specific DNA damage response regulators such as PARP1, ATR, and RAD51, confirming known synthetic lethal relationships and validating our methodology. Beyond BRCA1, we identify novel interactions, such as synthetic lethality between TP53 mutations and replication stress response genes, suggesting broader therapeutic targets [2].

Further experimental validation in TNBC cell lines confirms the functional impact of several of these synthetic lethal pairs, demonstrating increased cell death and impaired DNA repair capacity upon co-inhibition [3,4]. These effects are not observed in non-TNBC or BRCA1-proficient cells, highlighting the specificity and therapeutic potential of these interactions. In parallel, transcriptomic analysis of tumor samples reveals that some driver gene mutations are associated with compensatory upregulation of DNA repair pathways, indicating adaptive responses that could be exploited through synthetic lethal targeting [5].

## Conclusion

In conclusion, this study identifies and characterizes synthetic lethal relationships between cancer driver genes and DNA repair pathways in triple-negative breast cancer, offering a mechanistic framework for the development of targeted therapies. By integrating genomic, transcriptomic, and functional data, we uncover both known and novel vulnerabilities in TNBC that may guide personalized treatment approaches. These findings support the clinical potential of synthetic lethality-based strategies to overcome the therapeutic limitations in TNBC and highlight the importance of DNA repair processes in shaping tumor response to genetic perturbations.

## Acknowledgment

None.

## Conflict of Interest

None.

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***Address for Correspondence:** Greefeld Warn, Department of Urology, University of California, San Francisco, USA; E-mail: warm.gree@gmail.com*



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