Project: BRCA1 and 53BP1 abnormalities in sporadic (non-hereditary) triple-negative breast cancer.
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Research area: Biomarkers

Project Summary

Normal cells carry two copies of the BRCA1 gene, one from the individual's mother and one from their father. In some individuals, one copy of the BRCA1 gene has a mutation that renders it inactive or nonfunctional. This gene variation is passed from parents to children, and is therefore called a hereditary mutation.

BRCA1 plays a significant role in cell repair. If a mutation is present, and only one "good" copy of the gene exists, there is no "safety net" if an error occurs in the remaining good copy. Cells that have lost both copies of BRCA1 lose their ability to repair DNA efficiently, and abnormal cell growth - or tumors - result.

Women with hereditary mutations in the BRCA1 gene have a greatly increased risk of developing breast cancer; the breast cancers that arise in these women overwhelmingly are characterized as "triple negative". As BRCA1 plays a critical role in DNA repair, it follows that BRCA1-associated triple negative breast cancers show a marked defect in DNA repair.
However, most women with triple-negative breast cancers do not have BRCA1 mutations, and recent evidence suggests that a subset of these non-hereditary

(sporadic) cancers may also have acquired defects in BRCA1-related DNA repair mechanisms. Research in our laboratory, sponsored by the TNBC Foundation, is aimed at better understanding the potential DNA repair defects present in these non-hereditary triple-negative breast cancers, which represent the majority of triple negative breast cancer.

We have recently found that a subset of sporadic triple-negative breast cancer have lost expression of a DNA repair protein called p53-binding protein-1 (53BP1). 53BP1 functionally interacts with BRCA1 to regulate how certain types of DNA damage are repaired. The effect of loss of 53BP1 greatly varies depending on whether BRCA1 is also functional or disrupted, and may significantly impact how these cancers respond to certain treatments. We are now working on determining 1) the mechanism by which 53BP1 levels are reduced in certain TNBC and 2) the impact of 53BP1 loss on DNA repair efficiency and sensitivity to DNA damaging agents in cancer cells with either intact or disrupted BRCA1 function.

By this approach we hope to gain new insight into how loss of 53BP1 affects repair pathways in TNBC, which will be a step in identifying new therapeutic strategies that can target 53BP1 loss in these cancers.

This work has led to several publications and forms the basis for a large grant application to the National Cancer Institute. Our research in this area would not be possible without funding from the TNBC Foundation, and we are extremely grateful to the Foundation and its members for their continued support. We are committed to eradicating triple-negative breast cancer, and are excited to be able to pursue this research.