Brca\textsuperscript{mut/WT} mammary glands are morphologically similar to wild-type mammary glands in young and aged mice. Credit: *Nature Communications* (2023). DOI: 10.1038/s41467-023-40956-w
A pioneering study led by Professor Ashok Venkitaraman from the Cancer Science Institute of Singapore (CSI Singapore) at the National University of Singapore and Dr. Mona Shehata from the University of Cambridge (UK) has uncovered vital insights into the distinct effects of BRCA2 mutations on breast tissue cells, shedding light on early breast cancer development in people with BRCA2 mutations.

The research was published in the journal *Nature Communications* on 25 August 2023.

Breast cancer is a serious concern for individuals with BRCA2 mutations, with approximately 70% of carriers developing the disease by age 80. While BRCA2's role in DNA repair and as a tumor suppressor in protecting the cells against DNA replication stress are well-documented, little is known about the pathways leading to breast cancer development in BRCA2 mutation carriers.

Prof Venkitaraman, corresponding author of the study and Director of CSI Singapore, commented, "Despite the high risk faced by BRCA2 mutation carriers in developing breast cancer, there is still a critical lack of understanding of how these mutations impact the various cell types in the mammary glands. Our study aims to unravel the earliest event preceding the formation of cancer within the breast tissue microenvironment to better design early intervention strategies."

A detailed investigation using long-term mammary organoid cultures revealed that healthy mammary glands are not predisposed to form lesions that precede tumors. However, when exposed to stress during DNA replication, the population of hormone receptor-negative (HR-) luminal cells significantly expanded. Interestingly, the expansion was especially robust among the mammary gland organoids harboring BRCA2 mutations.
The study also discovered that HR- luminal cells with BRCA2 mutation exhibited enhanced organoid formation and survival under replication stress.

Further analysis at the single-cell RNA-sequencing level identified elevated stemness markers and type I interferon responses in these cells, which preferentially favors the growth of HR- luminal cells. It also showed that HR- luminal BRCA2-mutant cells became more susceptible to tumor formation only after multiple stresses, suggesting that distinct mechanisms drive the transformation of HR- and HR+ tumors, specifically in BRCA2 mutation carriers.

Understanding the mechanisms that drive early cancer development is crucial for classifying breast cancers into their distinct subtypes (triple-negative breast cancers, and hormone positive and HER2 positive breast cancers, among others), so that targeted, early treatment can be administered to achieve positive outcomes.

The team hopes to further validate their key observations from this study in mammary glands from preventive mastectomy cases among BRCA2 carriers. This will bolster their evidence to design early intervention strategies, which will provide guidance to clinicians caring for individuals with BRCA2 mutations.
