News Release

Iron-catalyzed oxidative stress compromises cancer promotional effect of BRCA2 haploinsufficiency through mitochondria-targeted ferroptosis

Key Points

- *Brca2* (+/-) rats revealed increased cancer incidence
- Fe-driven oxidative stress did not elevate cancer risk in *Brca2* (+/−) rats
- *Brca2* (+/−) normally increases cytoplasmic Fe, leading to initial ferroptosis resistance
- Chronic Fe overload induced ferroptosis sensitivity via mitochondrial dysfunction

Summary

A research team led by Dr. Shinya Toyokuni and graduate student Yuki Maeda from the Department of Pathology and Biological Responses at Nagoya University Graduate School of Medicine, in collaboration with Professor Tomoji Mashimo at the Institute of Medical Science, the University of Tokyo, has uncovered a surprising and paradigm-shifting result: oxidative stress caused by iron overload does not promote cancer in the context of BRCA2 mutations. This discovery challenges previous assumptions and provides new mechanistic insights into how BRCA2-related cancer develops—or is, in fact, suppressed—under oxidative stress conditions.

The study, published in the international journal *Redox Biology* on June 24, 2025, demonstrates for the first time that BRCA2-deficient cells are not more vulnerable to iron-catalyzed oxidative stress, but rather develop a resistance to ferroptosis in the early phase and ultimately undergo ferroptosis in later phases, effectively suppressing carcinogenesis.

Background

Cancer remains the leading cause of death in Japan. While therapeutic innovations continue to improve outcomes, preventing cancer by understanding its root causes is equally vital. Approximately 10% of breast and ovarian cancers are hereditary, and among Japanese individuals, BRCA2 mutations are the most common genetic predisposing factor. The BRCA2 gene plays a critical role in repairing DNA damage, and mutations in this gene increase lifetime cancer risk by compromising

genomic stability. As a result, risk-reducing surgeries such as mastectomy and oophorectomy are often recommended.
However, despite the gene's clinical importance, the precise molecular mechanisms by which BRCA2 mutations lead to cancer remain largely unknown. In particular, the contribution of environmental triggers like oxidative stress has been controversial. Compounding this challenge is the lack of appropriate animal models that faithfully reproduce human BRCA2-associated carcinogenesis.
To address this gap, the research team developed a novel rat model with a heterozygous BRCA2 mutation (T1942Kfs/+), mimicking the human condition. Using this model, they tested whether oxidative stress induced by iron overload—known to produce DNA damage via the Fenton reaction—could promote cancer development in BRCA2-deficient animals.

Research Findings

1. A BRCA2-mutant rat model that mimics human spontaneous tumorigenesis

Over a two-year observation period, rats carrying the BRCA2 mutation spontaneously developed malignant tumors at a rate of 36.8%, significantly higher than the 5.3% observed in wild-type animals. This finding confirms the validity of the model in recapitulating human hereditary cancer risk.

2. Iron-induced renal cancer was not promoted in BRCA2-mutant rats

When iron was administered intraperitoneally in the form of ferric nitrilotriacetate (Fe-NTA) to induce oxidative stress and renal carcinogenesis, no difference in tumor incidence, progression speed, or malignancy grade was found between wild-type and BRCA2-mutant rats. This sharply contrasts with previous studies using BRCA1-mutant rats, in which iron accelerated tumor formation, highlighting a key mechanistic divergence between BRCA1 and BRCA2 deficiencies.

3. Early iron exposure enhances antioxidant responses and confers ferroptosis resistance

Short-term (single or one-week) iron treatment of BRCA2-mutant rats revealed a suppressed lipid peroxidation response and reduced ferroptosis, indicating that these animals acquire resistance to ferroptosis through enhanced antioxidant systems. This protective mechanism was confirmed at the molecular level by elevated levels of xCT, GPX4, and NRF2, which counteract oxidative damage.

4. Prolonged iron exposure triggers ferroptosis and eliminates pre-cancerous cells

Interestingly, extended iron administration (three weeks) led to the opposite effect. The BRCA2-mutant rats accumulated catalytic Fe(II) within mitochondria, causing mitochondrial damage and increased lipid peroxidation. These conditions activated ferroptosis—a form of iron-dependent cell death—which eliminated potentially cancerous cells. Simultaneously, a compensatory increase in cell proliferation was observed, likely aimed at maintaining kidney tissue integrity. Notably, ferroptosis in this context served as a tumor-suppressive mechanism, offsetting the genomic instability associated with BRCA2 deficiency.

Significance and Future Perspectives

This study provides the first direct evidence that iron-catalyzed oxidative stress does not accelerate tumor development in BRCA2 mutation carriers—instead, it may activate ferroptosis to suppress it. These findings represent a major shift in our understanding of the role of oxidative stress in BRCA2-driven carcinogenesis and highlight fundamental differences from BRCA1-related cancer mechanisms.

Clinically, the results suggest that BRCA2 carriers may not require excessive avoidance of oxidative stressors such as radiation or certain diagnostic imaging procedures, as has often been presumed. Moreover, the ability of ferroptosis to eliminate damaged cells in BRCA2-deficient tissue opens up potential therapeutic avenues for cancer prevention or treatment by selectively inducing ferroptosis.

In conclusion, iron is a double-edged sword in cancer biology—it can cause DNA damage and promote carcinogenesis, but under certain genetic contexts like BRCA2 haploinsufficiency, it may paradoxically protect against cancer by triggering ferroptosis. This nuanced view of oxidative stress and genetic susceptibility is a step forward toward more individualized and mechanistically informed cancer prevention strategies.

Publication

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