News Release

Iron-Stress–Surviving Karyomegalic Cells Form a Niche for Kidney Cancer Initiation

Spatial transcriptomics reveals BRCA1-linked ferroptosis resistance during early carcinogenesis

Key Points

- Under severe iron-driven oxidative stress, a subset of renal proximal tubular cells that would normally be eliminated survives as cells with markedly enlarged nuclei, termed karyomegalic cells.
- BRCA1 haploinsufficiency expands a karyomegalic state associated with mitochondrial dysfunction, ferroptosis resistance, and activation of oncogenic programs including Myc, Met, and Lcn2.
- Related iron-handling and survival-biased programs extend into neighboring non-karyomegalic epithelial and stromal cells, creating a spatially organized pre-neoplastic niche rather than an isolated cellular abnormality.
- Quantitative nuclear morphology may serve as a functional histological readout of adaptation to exposome-related oxidative stress and help identify tissues at risk of malignant transformation.

Summary

A research team led by Yingyi Kong, M.D., Ph.D., Designated Assistant Professor, and Shinya Toyokuni, M.D., Ph.D., Professor Emeritus, of the Department of Pathology and Biological Responses, Nagoya University Graduate School of Medicine, has identified a spatially organized population of epithelial cells with enlarged nuclei that survives iron-driven oxidative stress and may establish a foothold for kidney cancer initiation. The research team also included Yukihiro Shiraki, M.D., Ph.D., Lecturer, and Atsushi Enomoto, M.D., Ph.D., Professor, of the Department of Tumor Pathology; Kazuhiro Furuhashi, M.D., Ph.D., Lecturer, and Shoichi Maruyama, M.D., Ph.D., Professor, of the Department of Nephrology, Nagoya University Graduate School of Medicine; and Tatsuhiko Imaoka, Ph.D., Director of the Department of Radiation Effects Research, Institute for Radiological Sciences, National Institutes for Quantum Science and Technology.

Iron is essential for life, but excess redox-active iron generates reactive oxygen species that damage DNA, lipids, and proteins. Damaged cells are normally removed through regulated cell-death pathways, including ferroptosis.

Cancer initiation, however, requires that a subset of injured cells evade this elimination. The location, morphology, and molecular programs of these stress-adapted survivor cells have remained unclear.

Using a ferric nitrilotriacetate-induced renal carcinogenesis model in wild-type and Brca1(L63X/+) rats, the researchers combined Xenium single-cell spatial transcriptomics, quantitative digital nuclear morphometry, mitochondrial analyses, and human cancer datasets. BRCA1 haploinsufficiency expanded karyomegalic proximal tubular cells characterized by mitochondrial dysfunction, hyperchromatic and remodeled nuclei, ferroptosis-resistant transcriptional features, and activation of Myc, Met, Lcn2, and iron-handling genes.

Importantly, neighboring cells without overt nuclear enlargement acquired related survival and iron-metabolic programs. This finding indicates that karyomegaly is not merely an isolated abnormality but a visible marker of a wider pre-neoplastic field involving epithelial and stromal cells. Analyses of TCGA kidney cancer data and BRCA1-mutant breast tissue further supported the clinical relevance of karyomegaly-associated gene modules and nuclear remodeling.

The study establishes quantitative nuclear morphology as a functional readout of oxidative-stress adaptation and suggests that mitochondrial adaptation and ferroptosis resistance may become targets for cancer prevention in genetically susceptible tissues. The article was accepted by Redox Biology on July 7, 2026, and was published online on July 8, 2026.

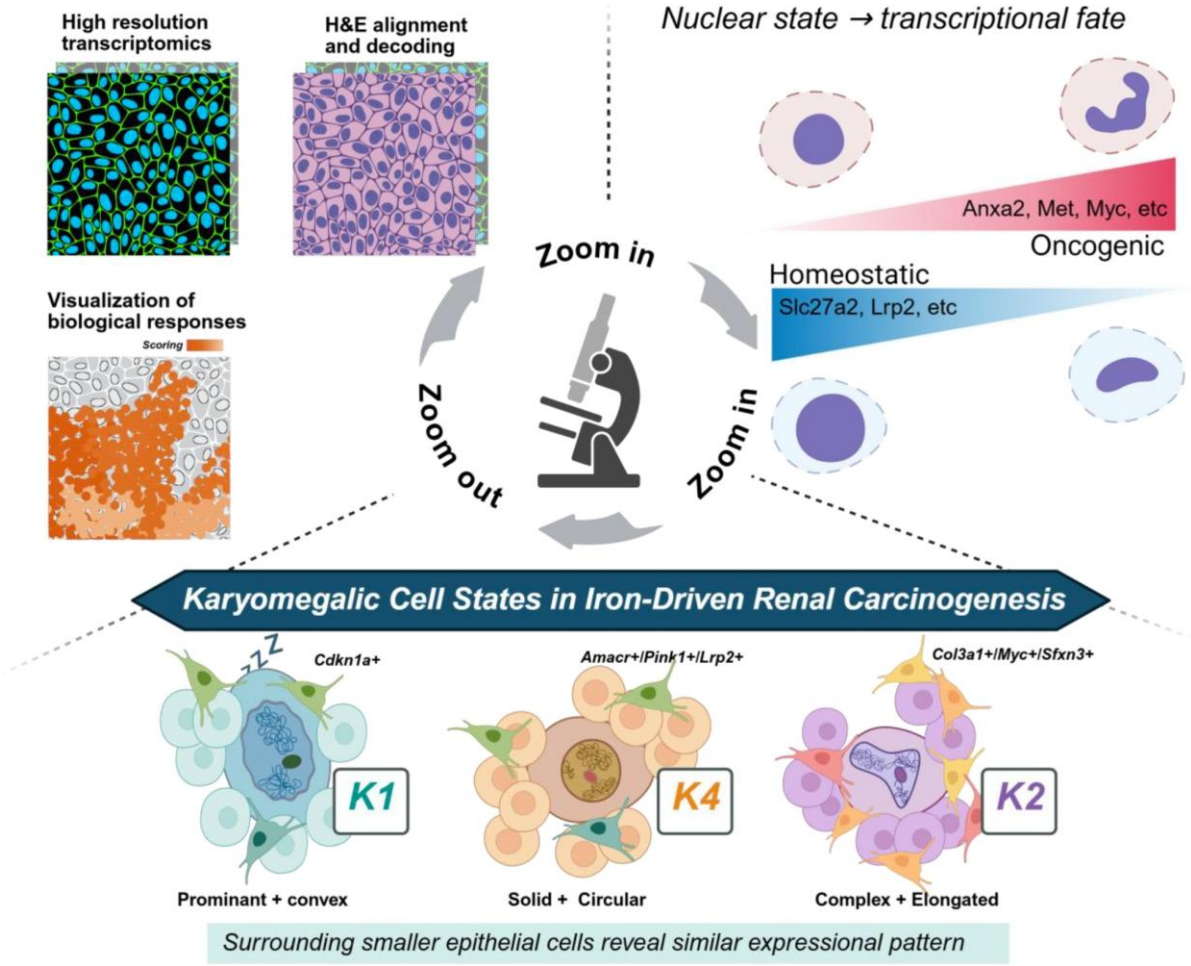

Figure 1. Conceptual overview. Spatial transcriptomics was aligned with H&E histology to connect nuclear morphology with gene expression in the same cells. Iron stress suppresses homeostatic programs while activating oncogenic programs, producing distinct karyomegalic states and a surrounding pre-neoplastic field.

Research Background

Iron supports oxygen transport, energy production, and DNA synthesis. Its redox activity, however, can catalyze the generation of reactive oxygen species. Chronic iron overload and iron-driven oxidative stress promote mutagenesis and malignant transformation. The totality of environmental, lifestyle, inflammatory, and metabolic exposures over a lifetime is referred to as the exposome. Iron-mediated oxidative stress provides a mechanistic link between such exposures and inherited cancer susceptibility.

Ferroptosis is a regulated form of cell death driven by iron-dependent lipid peroxidation. During early carcinogenesis, ferroptosis can eliminate heavily damaged cells. Tumor initiation may therefore depend on rare epithelial cells that adapt to oxidative injury and escape ferroptotic elimination. Until now, the

spatial identity and histological appearance of these survivor cells had not been clearly defined.

BRCA1 is a tumor-suppressor gene involved in DNA repair and chromosomal stability. The research group previously showed that Brca1 haploinsufficiency accelerates Fe-NTA-induced renal carcinogenesis and is accompanied by early c-Myc amplification and mitochondrial abnormalities. In the current study, the team sought to identify the stress-adapted epithelial states that emerge before overt tumor formation.

Research Methods

- Wild-type and Brca1(L63X/+) male rats were exposed to ferric nitrilotriacetate (Fe-NTA), and kidneys were analyzed at baseline and at one and three weeks after exposure.
- A custom 50-gene Xenium In Situ panel profiled renal cell identity, iron handling, mitochondrial programs, ferroptosis, and oncogenic signaling at single-cell spatial resolution.
- The same tissue sections were subsequently stained with hematoxylin and eosin, enabling precise alignment of molecular signals with histopathology.
- Nuclear area, eccentricity, circularity, solidity, convexity, boundary irregularity, and chromatin optical density were quantified and integrated with gene expression.
- Mitochondrial ultrastructure and respiratory function were assessed independently, and human relevance was evaluated using TCGA datasets and BRCA1-mutant breast tissue.

Research Results

1. Iron stress remodels proximal tubular cells from homeostasis toward stress adaptation

After Fe-NTA exposure, proximal tubular cells lost homeostatic transport and mitochondrial programs, including Slc27a2, Lrp2, Amacr, and Pink1. In contrast, Myc, Met, Lcn2, Anxa2, and genes involved in iron handling were induced, indicating a shift from normal tubular function toward injury adaptation and oncogenic signaling.

2. BRCA1 haploinsufficiency links nuclear enlargement to mitochondrial dysfunction and ferroptosis resistance

Brca1-mutant kidneys contained more proximal tubular cells with enlarged, hyperchromatic, elongated, and irregular nuclei. These cells exhibited transcriptional features of DNA-damage adaptation, altered iron metabolism,

mitochondrial dysfunction, and resistance to lipid-peroxidation-driven cell death. Independent respiratory assays confirmed impaired mitochondrial respiration and reduced metabolic flexibility.

3. Distinct karyomegalic states occupy different biological niches

Subclassification revealed several karyomegalic states, including quiescent or cell-cycle-arrested cells, cells retaining partial metabolic homeostasis, and a morphologically complex population enriched for Myc, Met, and Lcn2. The BRCA1-associated K2 state preferentially localized within a pro-oncogenic epithelial–stromal microenvironment containing Myc- and Sfxn3-expressing stromal cells.

4. Karyomegaly marks a broader pre-neoplastic field

Neighboring proximal tubular cells without overt nuclear enlargement displayed similar iron-handling and survival-biased transcriptional programs. Thus, karyomegalic cells act as a histological beacon for a wider tissue field undergoing early malignant adaptation, rather than representing an isolated phenotype.

5. Human datasets support clinical relevance

In TCGA clear-cell renal carcinoma data, karyomegaly-associated and ferroptosis-resistance gene-module scores in tumor-adjacent non-tumorous tissue and tumors were associated with clinical outcome. In BRCA1-mutant breast tissue, ductal epithelial nuclei showed altered elongation and morphology compared with wild-type tissue, supporting a link between hereditary susceptibility and nuclear remodeling.

Research Summary and Future Perspective

This study connects a classic histopathological feature—nuclear enlargement and irregularity—to specific stress-adaptive molecular programs at single-cell spatial resolution. Nuclear morphology may therefore contain functional information about mitochondrial failure, ferroptosis resistance, and early oncogenic selection.

The findings support a model in which exposome-related iron stress and BRCA1-linked hereditary susceptibility cooperate to produce epithelial survivor states and a supportive pre-neoplastic niche. Future studies will determine whether blocking mitochondrial adaptation or restoring ferroptosis sensitivity can prevent tumor initiation and whether quantitative nuclear morphology can aid early detection or risk stratification in human tissues.

The spatial transcriptomic component was an exploratory analysis using representative specimens and a restricted 50-gene panel, and the study primarily used a preclinical male rat model. Single-cell statistical associations should therefore not be interpreted as animal-level biological replication. Their biological relevance is supported by independent mitochondrial experiments, prior Fe-NTA studies, TCGA analyses, and human tissue morphometry.

Researcher Comment

“Pathologists have long recognized enlarged and irregular nuclei as warning signs of malignant transformation. What has been difficult to explain is what these shapes mean biologically. Our study suggests that karyomegaly reflects mitochondrial dysfunction and ferroptosis resistance in cells that survive iron stress, while also signaling that a broader pre-neoplastic field is forming around them. By identifying the earliest intersection between environmental exposure and inherited susceptibility, we hope to develop new approaches to cancer prevention.”

— Shinya Toyokuni and Yingyi Kong

Publication

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