Protected from a form of cell death, women are more resilient to kidney disease

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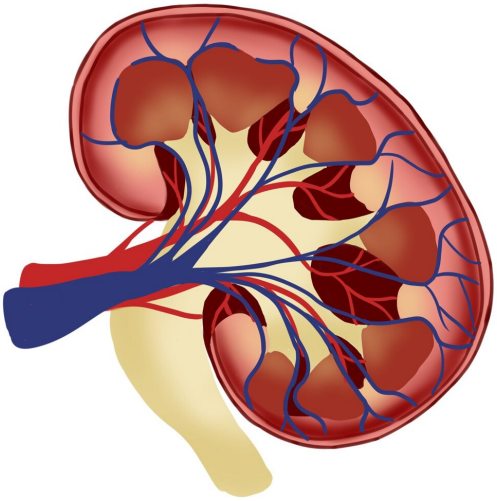

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In the battle of the sexes, women beat men in their ability to recover from kidney injury, but the reasons are not well understood.

A study led by Duke Health researchers provides some insights: Females, it turns out, have an advantage at the molecular level that protects them from a form of cell death that occurs in injured kidneys. This protection could be exploited as a potential therapeutic.

The findings appear online Nov. 8 in the journal Cell Reports.

"Kidney disease afflicts more than 850 million people worldwide every year, so it's important to understand why female kidneys are more protected from these acute and chronic injuries," said Tomokazu Souma, M.D., Ph.D., assistant professor in the Department of Medicine at Duke University School of Medicine. "Our study is a step toward identifying the causes and suggests that this female resilience could be therapeutically harnessed to improve kidney repair in both sexes."

Souma and colleagues conducted studies in mice focusing on a form of cell death called ferroptosis, which was only recently discovered. This form of cell death is dependent on iron and oxidative stress. It has been identified as a key player in kidney diseases.

Using genetic and single-cell RNA transcriptomic analysis in mice, the researchers found that being female confers striking protection against ferroptosis through a particular pathway called nuclear factor erythroid 2–related factor 2, or NRF2.

In females, NRF2 is highly active, keeping cell death in check. In males, however, the sex hormone testosterone reduces the activity of NRF2, thus promoting ferroptosis and undermining cell resiliency in kidney injury.

Further experiments showed that chemically activating NRF2 protected male kidney cells from ferroptosis, demonstrating that NRF2 could be a potential therapeutic target to prevent failed renal repair after acute kidney injury.

"By identifying the mechanism in which the female hormonal environment protects and the male hormonal environment aggravates acute and chronic kidney injuries, we believe there is strong potential to boost the resilience of kidneys," Souma said.

In addition to Souma, study authors include Shintaro Ide, Kana Ide, Koki Abe, Yoshihiko Kobayashi, Hiroki Kitai, Jennifer McKey, Sarah A. Strausser, Lori L. O'Brien, Aleksandra Tata, and Purushothama Rao Tata.

More information: Tomokazu Souma, Sex differences in resilience to ferroptosis underlie sexual dimorphism in kidney injury and repair, *Cell*

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