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Estrogens protect against acute kidney injury

Hormone-dependent protection of the kidneys via multiple defense mechanisms against ferroptosis / Recent findings published in Nature / Broad implications for clinical applications

Acute kidney injury occurs frequently and still represents a major clinical challenge due to the lack of a targeted therapy. For decades, clinicians have observed that women are less susceptible to acute kidney failure than men. This is not a new finding; in fact, this has been reported as early as 1940 and was confirmed in epidemiological studies. However, to this day, the underlying cause of this effect remains a mystery. In a paper recently published in Nature, scientists at the Medical Faculty Mannheim, Heidelberg University have now provided a key, novel explanation for this phenomenon.

In the study, they focused on the female sex hormone estrogen and the process of ferroptosis, an iron-dependent form of regulated cell death. They discovered that estrogen blocks ferroptosis, explaining how the protective effect on the kidneys is lost with menopause when sex hormone production declines. Interestingly, estrogen and specifically its hydroxylated derivatives - such as 2-hydroxyestradiol - are key mediators of a complex

Photograph

Professor Dr. Andreas Linkermann and two of the three first authors of the work published in the journal Nature: Shubhangi Gavali, PhD (left) and Francesca Maremonti, PhD.

Publication

Tonnus, W., Maremonti, F., Gavali, S. et al.
Multiple oestradiol functions inhibit ferroptosis and acute kidney injury.
DOI: 10.1038/s41586-025-09389-x
News and Views: Oestrogen defends against kidney damage caused by iron-dependent cell death
DOI: 10.1038/d41586-025-02422-z
Nature (2025)

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protective mechanism through genomic and non-genomic mechanisms.

Remarkably, estrogen acts like an intrinsic protective drug against ferroptosis by itself. Additionally, by binding to its receptor, estrogen initiates various biological systems that can be considered defense mechanisms against ferroptosis, including the regulation of hydropersulfides, which act as radical scavengers to keep ferroptosis in check. Estrogen receptor engagement additionally counteracts the alteration of ether lipids - important components of the cell membrane - thereby also inhibiting ferroptosis.

These observations are key findings to explain the differences for kidney disease risks observed between males and females, and are interesting starting points for novel therapeutic approaches. But there´s more than that! Ferroptosis also plays a key role in many different diseases. "Our findings may also have implications far beyond the kidney, even for cancer research. These results bring ferroptosis into the focus of gender differences for conditions such as heart attacks and stroke from which women tend to be more protected than men, and even the well-known longer life expectancy of women," explains Professor Andreas Linkermann, Director of the 5th Department of Medicine at the University Medical Center Mannheim and last author of the publication.

The potential implications of this work for other diseases and in other contexts are difficult to assess at this stage. Ethical issues may also have to be considered, for example in the context of transplant medicine, where the question could arise as to whether organs from female donors – before menopause – are “more

valuable” than those from male donors because they are less susceptible to the surgical process of organ transfer. “The significance of ferroptosis is actually opening up a whole new field of research,” concludes Andreas Linkermann.

News and Views

Tom Vanden Berghe, a worldwide expert in this field, has also recognized the great implications of the findings of the nephrologists and scientists based in Mannheim, conducting research at Heidelberg University. In Vanden Berghe`s “News and Views” article, published in the same issue of Nature under the title “*Oestrogen defends against kidney damage caused by iron-dependent cell death*,” he draws the following conclusion:

"This work represents a milestone in our understanding of sex differences in acute kidney failure and expands the physiological relevance of ferroptosis beyond cancer and neurodegeneration. Importantly, these findings may help explain the increased vulnerability to acute kidney injury in postmenopausal women and provide a rational basis for exploring estrogenic metabolites or ferroptosis inhibitors as therapeutic agents. As ferroptosis gains traction as a unifying mechanism of tissue injury, this study underscores the importance of sex as a biological variable in its regulation."