

## PRESS RELEASE

### Ominous false alarm in the kidney

Bonn researchers reveal how a tiny RNA molecule in the kidney triggers a deadly autoimmune disease

**Bonn, November 3 – Researchers at the University Hospital Bonn (UKB) and the University of Bonn have discovered how a small, naturally occurring RNA molecule in the kidney activates a mutated immune receptor, triggering a chain reaction. In cooperation with Nanyang Technological University Singapore and the University Hospital Würzburg, among others, the study provides an explanation for how a point mutation in the immune receptor RIG-I transforms the body's defense system into a self-destructive force and causes severe organ-specific autoimmune diseases. The results have now been published in the journal Science Immunology.**

RIG-I is an important sensor in the innate immune system that recognizes viral RNA and activates the antiviral defense. However, certain changes in the genetic material, known as mutations, can make RIG-I hypersensitive, causing the immune receptor to mistake the body's own RNA for viral intruders. The research team found that mice carrying a RIG-I E373A mutation associated with patients spontaneously developed lupus-like nephritis, a severe and often fatal kidney inflammation. In contrast to classic lupus, in which inflammation occurs due to deposits of immune complexes, the disease in these mice was caused by direct kidney inflammation triggered by the mutated RIG-I.

#### Hidden, tissue-specific activator of autoimmune inflammation

Further investigations showed that a short, non-coding RNA known as Y-RNA, which is produced in large quantities in the kidney, binds directly to the mutated RIG-I and triggers its abnormal activation. "We discovered that Y-RNA acts like a false alarm for the mutated RIG-I receptor, especially in kidney cells," says corresponding author Prof. Hiroki Kato, Director of the Institute for Cardiovascular Immunology at UKB and member of the ImmunoSensation<sup>2</sup> Cluster of Excellence at the University of Bonn. "This local malfunction of the immune system triggers severe inflammation similar to human lupus nephritis."

#### From molecular insights to the disease mechanism

"Using advanced molecular and structural analyses, we were able to show that the RIG-I-E373A mutant binds to Y-RNA in an unusual way, which leads to activation of the receptor even without viral infection," says first author Saya Satoh, a doctoral student at the University of Bonn in Prof. Kato's research group at the UKB. "This abnormal activation caused the kidney cells to produce large amounts of interferons and chemokines, which attracted

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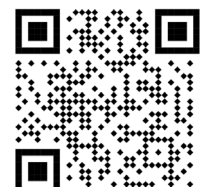
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immune cells and triggered inflammation." However, the researchers were also able to identify a potential therapeutic target: blocking the so-called CCR2 signaling pathway, which recruits monocytes belonging to the white blood cells, significantly reduces kidney inflammation in the affected mice.

### **Impact on autoimmune diseases**

Mutations in RIG-I have been linked to rare hereditary diseases such as Singleton-Merten syndrome (SMS) and systemic lupus erythematosus (SLE). This study provides important insights into how such mutations can selectively damage organs such as the kidney. These findings could pave the way for the development of targeted therapies that block the activation of mutated RIG-I or its interacting Y RNAs.

### **Participating institutions and funding:**

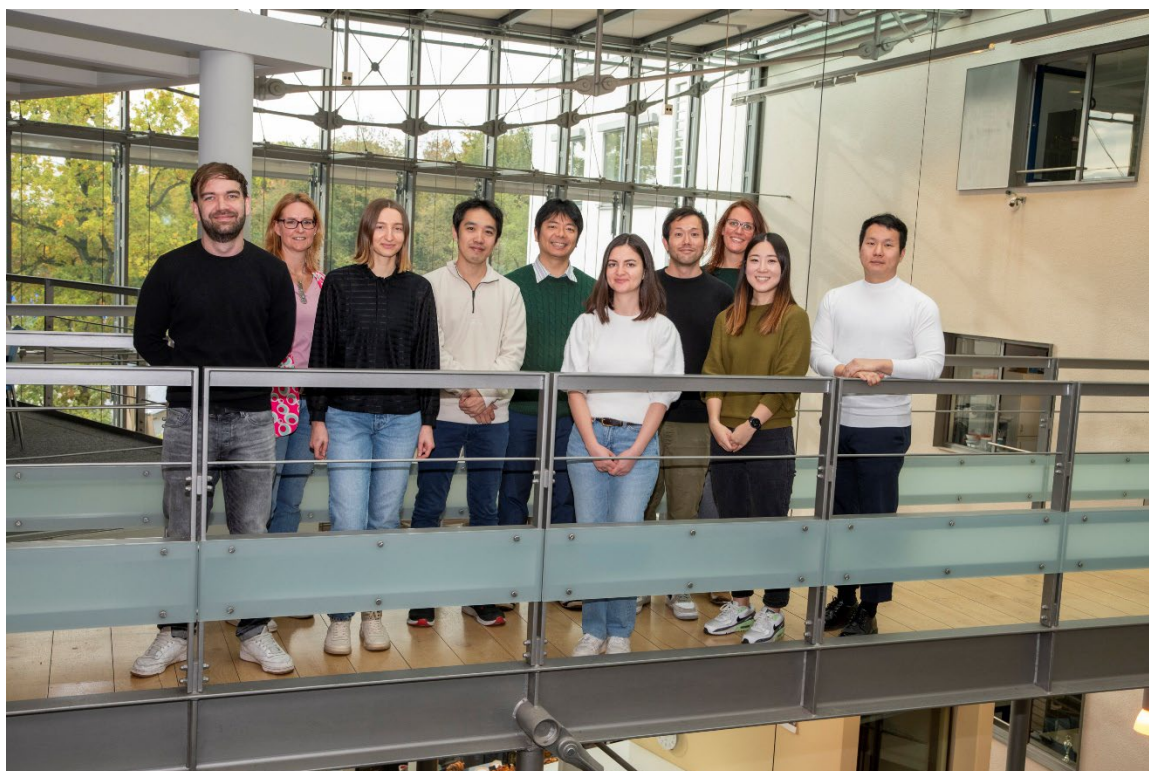
In addition to the UKB and the University of Bonn, the following institutions were involved in the study: Nanyang Technological University, Singapore, University Hospital Würzburg, Germany, Okayama University, Japan, Kyoto University, Japan. The project was supported by the DFG, the German Excellence Strategy EXC 2151 "Nucleic Acid Immunity – Collaborative Research Center TRR237," Open Philanthropy as part of the PANDEMIC ANTIVIRAL DISCOVERY PARTNERSHIP, and the Singapore Ministry of Education MOE AcRF Tier 1 Award.

**Publication:** Saya Satoh et al.: Local activation of mutant RIG-I by short non-coding Y-RNA in the kidney triggers lethal nephritis; Science Immunology; DOI: <https://doi.org/10.1126/sciimmunol.adx1135>

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### **Image material:**



**Caption: Molecular mechanism for fatal nephritis elucidated:** Prof. Hiroki Kato's team has discovered how small RNA molecules activate the mutated viral sensor RIG-I and lead to fatal nephritis.

Image credit: University Hospital Bonn (UKB)

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**About the University Hospital Bonn:** As one of Germany's leading university hospitals, Bonn University Hospital (UKB) combines excellence in medical care and research with high-quality teaching. Every year, UKB treats more than half a million outpatients and inpatients. Around 3,500 students are enrolled in medicine and dentistry, and over 600 individuals receive training in healthcare professions annually. With around 9,900 employees, UKB is the third-largest employer in the Bonn/Rhein-Sieg region. In the „Focus hospital rankings“, UKB is rated the top university hospital in North Rhine-Westphalia and has the second-highest case mix index (an indicator of treatment complexity) of all university hospitals nationwide. In 2024, UKB secured nearly €100 million in third-party funding for research, development, and teaching. For the fourth consecutive year, the F.A.Z. Institute recognized UKB as both “Germany's Training Champion” and “Germany's Most Desirable Employer.” For current figures and further information, please refer to the annual report at:

[geschaeftsbericht.ukbonn.de](https://geschaeftsbericht.ukbonn.de)