Hôpital général juif
Jewish General Hospital

McGill

INSTITUT LADY DAVIS DE RECHERCHES MÉDICALES | LADY DAVIS INSTITUTE FOR MEDICAL RESEARCH

PAPER OF THE MONTH • FEBRUARY 2026

Siqi Liu, BSc

Master's student in Clinical and Translational Research, McGill University

Sofiya Tsyplenkova, MSc

Former master's student in Microbiology and Immunology, McGill University

Current position: Research Assistant, Montreal Neurological Institute-Hospital

Carine Fillebeen, PhD

Research Associate, Lady Davis Institute for Medical Research

Kostas Pantopoulos, PhD

Senior Investigator, Lady Davis Institute for Medical Research

Professor, Department of Medicine, McGill University

blood®

Tfr2 is necessary for acute iron-dependent hepcidin induction in mice with Tfr1-deficient hepatocytes

Siqi Liu, Sofiya Tsyplenkova, Edouard Charlebois, Daniel Frederick Wallace, V Nathan Subramaniam, Carine Fillebeen, and Kostas Pantopoulos

Iron is essential for life, but excess iron is toxic. The liver maintains iron balance by producing hepcidin, a hormone that limits iron absorption and distribution in the body. When iron levels rise, hepcidin increases; when iron is scarce, it decreases. However, the precise mechanisms by which liver cells sense iron and activate hepcidin have remained unclear.

In this study, we investigated the roles of transferrin receptor 1 (Tfr1) and transferrin receptor 2 (Tfr2) in iron uptake and iron sensing. Using genetically engineered mice lacking Tfr1, Tfr2, or both specifically in hepatocytes, we uncovered several unexpected findings.

Thus, mice with hepatocyte-specific disruption of both Tfr1 and Tfr2 are viable and even develop iron overload (hemochromatosis) due to hepcidin deficiency. Notably, iron overload is milder compared to that observed in mice lacking only Tfr2 in hepatocytes. Our data demonstrate that hepatocytes can obtain sufficient iron through alternative pathways and can only utilize Tfr1 but not Tfr2 for the uptake of transferrin-bound iron.

Most importantly, we found that Tfr2 is essential for triggering hepcidin production in response to a sudden rise in dietary iron. Even when another regulator, the hemochromatosis protein Hfe, became fully active due to lack of its repressor Tfr1, acute hepcidin activation failed in the absence of Tfr2. However, de-repressed Hfe stimulated hepcidin expression in response to chronic dietary iron intake, mitigating iron overload in mice with combined loss of Tfr1/Tfr2 vs loss of only Tfr2 in hepatocytes. These data suggest that Tfr2 and Hfe have non-overlapping functions under chronic iron loading but act cooperatively to induce hepcidin after acute iron exposure.

https://doi.org/10.1182/blood.2025030054