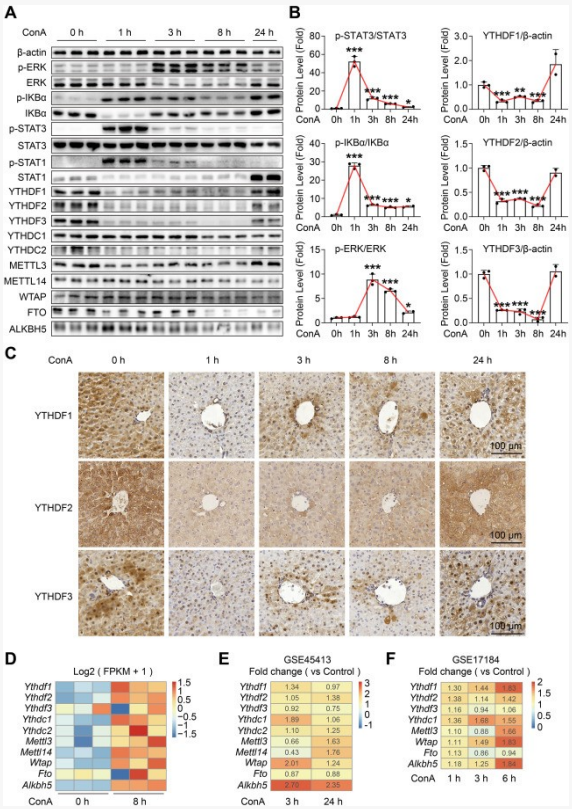
YTHDF1 Identified As a Potential Therapeutic Target for Autoimmune Hepatitis

New Study Underscores The Pivotal Role Of YTHDF1 In Immune-Mediated Hepatitis

CHINA, April 2, 2025 /EINPresswire.com/ -- Autoimmune hepatitis (AIH) is a severe autoimmune disease characterized by immune-mediated hepatocyte destruction, leading to hepatic necroinflammation, cirrhosis, and potential fatality. N6-methyladenosine (m6A), a prevalent post-transcriptional mRNA modification, dynamically regulates various cellular processes. However, the relationship between AIH and m6A and its regulators remains poorly understood.



(A, B) Immunoblot analysis of liver tissues with m6A family and representative inflammatory pathway antibodies (A), followed by gray analysis using Image J (B). (C) Representative images of liver sections for immunostaining analysis with YTHDF1, YTHDF2 an

This research, published in the Genes & Diseases journal by a team from Xiamen University, addresses the role of m6A and its regulators in T cell-mediated hepatitis.

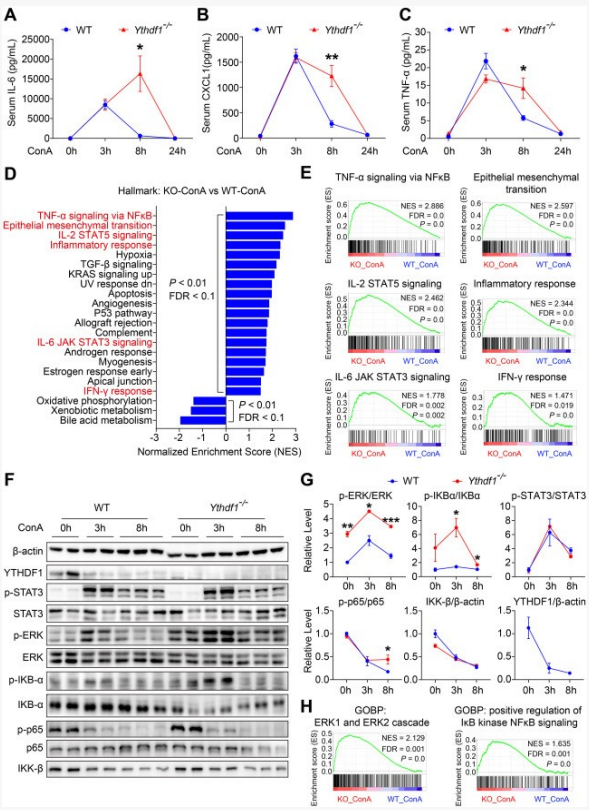
In this study, the researchers utilized concanavalin A (ConA)-induced mouse liver damage as an experimental model for T cell-mediated hepatitis. Initial investigations revealed that the protein expression of m6A readers, YTHDF1, YTHDF2, and YTHDF3, during the early stage of ConA-induced hepatitis was dramatically decreased in the liver. Notably, YTHDF1-deficient (Ythdf1−/−) mice showed more susceptibility to ConA-induced liver injury, along with an intensified inflammatory storm accompanied by an aggravated hepatic inflammatory response via ERK and nuclear factor-kappa B (NF-κB) pathways.

This study not only highlights the crucial role of YTHDF1 in hematopoietic cells in suppressing T cell-mediated liver injury but also suggests an immunomodulatory and anti-inflammatory role for YTHDF1 in T cell-mediated hepatitis. Furthermore, Ythdf1−/− mice exhibited higher serum

levels of proinflammatory cytokines upon ConA challenge, indicating that YTHDF1 deficiency sensitizes inflammatory cells to ConA, intensifying cytokine production and exacerbating hepatic inflammation. Interestingly, the activation of the NF-κB pathway and MAPKs signaling after ConA treatment in Ythdf1−/− mice further emphasizes the role of YTHDF1 in suppressing inflammatory responses.

Additionally, immunohistochemical staining results revealed significantly higher CD4+ cell numbers in the ConA-treated Ythdf1−/− mice livers than in wild type mice, implying that YTHDF1 deficiency could increase the infiltration and activation of inflammatory cells. Furthermore, this study demonstrates that YTHDF1 deletion in macrophages exacerbates lipopolysaccharide-induced inflammatory responses, emphasizing the necessity of YTHDF1 in immune cells for an effective inflammatory response.

In summary, this study uncovered that YTHDF1 deficiency exacerbates the immune response in ConA-induced hepatitis by modulating the expression of inflammatory mediators, highlighting the potential of YTHDF1 as a promising therapeutic target for clinical hepatitis.



(A–C) Serum samples collected at 0 h, 3 h, 8 h, and 24 h after ConA (8 mg/kg) injection from Fig. 2B and C was measured for IL-6 (A), CXCL1 (B), and TNF-α (C) levels, n = 3–5 per group. (D) Liver tissues of Ythdf1−/− (KO) and WT mice collected at 8 h aft

Reference

Title of Original Paper: YTHDF1 shapes immune-mediated hepatitis via regulating inflammatory cell recruitment and response

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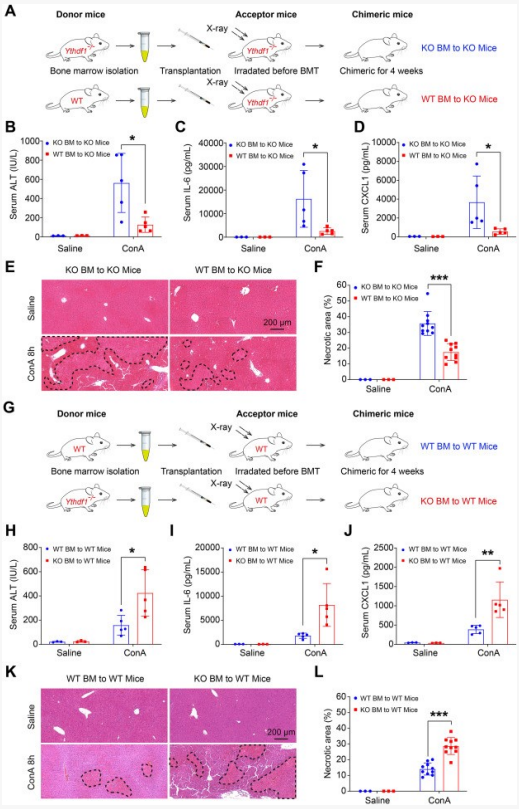

(A–F) Eight weeks old male Ythdf1−/− mice (KO) were irradiated with 8 Gy X-rays, and 6 h later, bone marrow cells (BM) from male donor Ythdf1−/− or WT mice were transplanted into the irradiated mice with an intravenous injection at a number of 200E4 cells

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