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The histone methyl-transferase Suv39h2 contributes to non-alcoholic steatohepatitis in mice

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Uncontrolled inflammatory response highlights the central theme of Non-Alcoholic Steatohepatitis (NASH), a growing global pandemic. Hepatocytes and macrophages represent two major sources of hepatic inflammation during NASH pathogenesis contributing to excessive synthesis of pro-inflammatory mediators. The epigenetic mechanism that accounts for the activation of hepatocytes and macrophages in this process remains obscure. Here we report that compared to Wild Type (WT) littermates, mice with a deficiency in the histone H3K9 methyl-transferase Suv39h2 (KO) exhibited a less severe form of NASH induced by feeding with High-Fat high-carbohydrate Diet (HFD). Pro-NASH stimuli increased Suv39h2 expression in cell culture, in mice, and in human livers. In hepatocytes, Suv39h2 bound to the Sirt1 gene promoter and repressed Sirt1 transcription. Suv39h2 deficiency normalized Sirt1 expression allowing NF-κB/p65 to become hypo-acetylated thus dampening NF-κB-dependent transcription of pro-inflammatory mediators. In macrophages, Suv39h2-mediated repression of PPARγ transcription favored a pro-inflammatory M1 phenotype over an anti-inflammatory M2 phenotype thereby elevating hepatic inflammation. It can be concluded that Suv39h2 plays a pivotal role in the regulation of inflammatory response in hepatocytes and macrophages contributing to NASH pathogenesis.

Biography

Zhiwen Fan has completed his MD degree in Nanjing Medical University in 2016 and currently working as the Director of Molecular Pathology Laboratory at Nanjing Drum Tower Hospital. His research field is majorly in the study of liver disease related transcriptional regulation, which was mainly through Post-Translational Modification (PTM) mediated fine tuning of transcription factors. He is the author of over 13 papers in reputed journals.

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