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Critical roles of the Histone methyltransferase MLL4 in metabolic syndrome

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The pathophysiologic continuum of non-alcoholic fatty liver disease begins with steatosis. Despite recent advances in our understanding of the gene regulatory program directing steatosis, how it is orchestrated at the chromatin level is unclear. PPAR γ 2 is a hepatic steatotic transcription factor induced by overnutrition. Here, we report that the histone H3 lysine 4 methyltransferase MLL4/KMT2D directs overnutrition-induced murine steatosis via its coactivator function for PPAR γ 2. We demonstrate that overnutrition facilitates the recruitment of MLL4 to steatotic target genes of PPAR γ 2 and their transactivation via H3 lysine 4 methylation because PPAR γ 2 phosphorylated by overnutrition-activated ABL1 kinase shows enhanced interaction with MLL4. We further show that Pparg2 (encoding PPAR γ 2) is also a hepatic target gene of ABL1-PPAR γ 2-MLL4. Consistently, inhibition of ABL1 improves the fatty liver condition of mice with overnutrition by suppressing the pro-steatotic action of MLL4. Our results uncover a murine hepatic steatosis regulatory axis consisting of ABL1-PPAR γ 2-MLL4, which may serve as a target of anti-steatosis drug development.

Biography

Seunghee Lee is working as a Professor at Seoul National University in South Korea.

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