

DUSP22 controls lysosomal degradation of fatty acid synthase by LYZ to prevent lipogenesis and obesity

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Induction of fatty acid synthase (FASN) occurs in obesity and obesity-related diseases. Dual-specificity phosphatase 22 (DUSP22, also named JKAP) is a negative regulator of T-cell signaling, inflammatory diseases, and cancer progression; however, the *in vivo* role of DUSP22 in metabolic syndrome remains unclear. We found that *Dusp22* KO mice spontaneously developed obesity and displayed high FASN levels in insulin-responsive tissues. Mechanistically, DUSP22 dephosphorylated FASN protein at three residues and enhanced the novel interaction between FASN and lysozyme C (LYZ), resulting in lysosomal degradation of FASN and subsequent suppression of *de novo* lipogenesis. Conversely, *Lyz1/Lyz2* double knockout mice manifested obesity with FASN induction in insulin-responsive tissues. Remarkably, several *FASN* or *LYZ* SNPs in human participants (n = 324,694 to 1,654,960) from UK biobank were correlated with BMI. Furthermore, 4 *DUSP22* and numerous *LYZ* gene variants from a US WES Cohort were also associated with overweight and obesity. All 4 *DUSP22* gene variants caused DUSP22 dysfunction and subsequent FASN stabilization. Collectively, DUSP22 cooperates with LYZ to induce FASN lysosomal degradation, preventing lipogenesis. Our findings identify LYZ and DUSP22 as pivotal regulators of fatty acid synthesis and implicate them in the regulation of human obesity.