Bile Acid Signaling Regulates Adipogenesis through Inhibition of RORγ

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Obesity associated disorders such as T2D, hypertension and CVD, commonly referred to as the “metabolic syndrome”, are prevalent diseases of industrialized societies. Deranged adipose tissue proliferation and differentiation contribute significantly to the development of these metabolic disorders. Comparatively little however is known, about how these processes influence the development of metabolic disorders. Retinoid-related orphan receptor γ (RORγ) is a newly identified regulator of adipogenesis, controlling insulin sensitivity in obesity. RORγ inhibits adipogenesis via its target gene matrix metallopeptidase 3 (MMP3) which emphasizes the importance of extracellular matrix structures in determining cell fate. We report here the identification of Ba1 an atypical bile acid derivative which functions as a an endogenous ligand for RORγ. Repression of RORγ activity via its ligand leads to alterations in the extracellular environment of adipocytes, thereby directly modulating the balance between adipocyte hyperplasia and hypertrophy. Activation of the adipogenic program in times of lipid overload leads to improved control of circulating free fatty acids, as well as protection from hyperglycemia and insulin resistance.