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A Secreted Protein Can Attenuate High Fat Diet Induced Obesity and Metabolic Syndrome in Mice

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Abstract : Obesity and its associated complications, such as insulin resistance and non-alcoholic fatty liver disease, are reaching epidemic proportions. In mice, the TGF-β superfamily is implicated in the regulation of white and brown adipose tissues differentiation. The Kielin/Chordin-like Protein (KCP) is a secreted regulator of the TGF-β superfamily pathways that can inhibit both TGF-β and Activin signals while enhancing the Bone Morphogenetic protein (BMP) signaling. However, the effects of KCP on metabolism and obesity have not been studied in animal models. Thus, we examined the effects of KCP loss or gain of function in mice that were maintained on either a regular or a high fat diet. Loss of KCP sensitized mice to obesity and associated complications such as hepatic steatosis and glucose intolerance. In contrast, transgenic mice that expressed KCP in the kidney, liver and adipose tissues were resistant to developing high fat diet induced obesity and had significantly reduced white adipose tissue. KCP over-expression was able to shift the pattern of Smad signaling in vivo, to increase the levels of P-Smad1 and decrease P-Smad3, resulting in resistance to high fat diet induced hepatic steatosis and glucose intolerance. In aging mice, loss of KCP promoted liver pathology even when mice were fed a normal diet. The data demonstrate that shifting the TGF-β superfamily signaling with a secreted inhibitor or enhancer can alter the physiology of adipose tissue to reduce obesity and can inhibit the initiation and progression of hepatic steatosis to significantly reduce the effects of high fat diet induced metabolic disease.

Keywords : adipose tissue, KCP, obesity, TGF-β, BMP, hepatic steatosis, metabolic syndrome
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