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Regulation of hepatic steatosis by targeted degradation of ceramide in the adipose and liver

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The adipose-derived factor adiponectin promotes substantial improvements in hepatic glucose and lipid metabolism, potently opposing steatosis. Many of these effects are recapitulated in transgenic mice possessing a secretion-incompetent adiponectin. Two adiponectin receptors have been identified, both possessing homology to Alkaline Ceramidase. These receptors convey ceramidase activity that can be further enhanced by adiponectin, which results in simultaneous decreases in ceramide and increases in the sphingoid bases: sphingosine, sphinganine, and sphingosine 1-phosphate. To evaluate the effects of adiponectin signaling within the adipocyte proper, we have generated tetracycline-inducible mice overexpressing, adiponectin receptor 1, adiponectin receptor 2, or acid ceramidase, selectively within the mature adipocyte of diet-induced obese mice and leptin-deficient mice. As, with secretion-incompetent adiponectin, all 3 of these adipocyte-restricted inducible models promote a substantial improvement in hepatic glucose and lipid metabolism, providing robust protection against hepatic steatosis. Driving these same transgenic models under the control of a liver-specific albumin promoter also recapitulates these improvements in the liver. Collectively, these data suggest that adiponectin, via enhancements in ceramidase activity within the adipocyte or the liver itself, may play a critical role in regulation of hepatic steatosis and hepatic glucose efflux, largely governed by the diminished accumulation of ceramides in the liver. Mechanistically, the curtailing of aberrant ceramide accumulation did not alter hepatic secretion or oxidation of lipid. Rather, lowering hepatic ceramide potently restricts hepatic lipid uptake. These effects appear governed by altered CD36 expression and localization to the plasma membrane in response to PKC zeta, which is strongly activated by ceramides.

Biography

Will L Holland completed his dissertation work at the University of Utah in 2007. During his subsequent Postdoctoral work, he uncovered the roles of adiponectin and FGF21 as potent regulators of sphingolipid metabolism. He is currently an Assistant Professor in the Touchstone Diabetes Center, focusing efforts on the roles of ceramide catabolic enzymes on glucose and lipid metabolism.

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