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Wnt5a protects against intracellular cholesterol accumulation through inhibition of the mevalonate pathway

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Adipose tissue is an easily accessible tissue that in addition to its roles in storage of excess energy in form of triglyceride also contains the largest pool of cholesterol in the body and plays a critical role in maintaining cholesterol homeostasis. The mechanism of this regulation is however unknown. We reported previously that LRP1, a trans-membrane receptor positively regulates a Wnt5a signaling pathway that protects against intracellular cholesterol and cholesteryl-esters accumulation in cells submitted to adipogenesis. To investigate the role of Wnt5a in cholesterol homeostasis we generated mice overexpressing Wnt5a in adipose tissue (aTgWnt5a). aTgWnt5a mice fed a regular chow diet exhibit a decrease in adipocyte cholesterol levels with no difference in triglycerides content compared to controls. This was accompanied by an inhibition in adipose tissue of the HMG-CoA reductase, the rate-limiting enzyme for cholesterol biosynthesis. mRNA and protein levels of HMG CoA reductase were both severely decreased compared to controls suggesting that Wnt5a interfere with cholesterol biosynthesis. In agreement with this hypothesis, we found an increase in Insig-1 protein and mRNA levels in adipocytes from these mice, with no difference in SREBPs mRNA expressions. We confirmed *in vitro* the effects of Wnt5a on the HMGCoA reductase levels. Similarly, Wnt5a increased Insig-1 protein when stably transfected in MEFs. In agreement with an inhibition effect of Wnt5a on cholesterol biosynthesis, SREBP2 cleavage, and nuclear translocation were reduced in Wnt5a transfected cells. These data suggested that Wnt5a protects against cholesterol intracellular accumulation through inhibition of its biosynthesis.

Biography

Philippe Boucher is professor of Physiology at University of Strasbourg. After a Ph.D. at the University of Lyon, France and a postdoctoral fellowship at UT Southwestern Medical Center at Dallas he became an Assistant Professor of Physiology at University of Strasbourg before moving on a Full Professor position. His lab aims to understand cell-signalling networks and, in more specific terms, how LRP1 and its partners impact on growth-promoting and differentiation signals that protect against disorders such as atherosclerosis and obesity. He has published more than 25 papers in reputed journals. His work has identified several fundamental molecular mechanisms by which these genes protect against atherosclerosis, heart failure, and maintain cholesterol homeostasis.

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