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Regulation of glucose homeostasis by adaptor proteins Nck

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Nck adaptor proteins, Nck1 and Nck2, exclusively composed of Src homology (SH) domains are well known to mediateintracellular signal transduction from activated plasma membrane receptor tyrosine kinases. Besides this, our group has recently reported a novel role forNck in mediating endoplasmic reticulum (ER) stress signaling through the unfolded protein response (UPR). In fact, Nck1 interacts with and modulates signaling from the UPR mediatorsIRE1α and PERK and the pathophysiological importance of this functionof Nck1was revealed when we uncovered that *Nck1* indirectly affects insulin signaling by promoting the IRE1α-JNK pathway involved in phosphorylating the insulin receptor substrate 1 (IRS-1) on its inhibitory site Ser^{307}. As a consequence, Nck1 knockout mice ($Nck1^{-/-}$) are protected from ER stress-mediated insulin resistance induced by high fat diet (HFD). However, although Nck1 and Nck2 share high level of identity and functionality, lean and obese $Nck2^{-/-}$ mice,in contrast to $Nck1^{-/-}$ mice,developed greater glucose intolerance and insulin resistance with aging compared to wild-type matched littermates. Consistent with this, hepatic insulin-induced Akt phosphorylation was drastically impaired in lean $Nck2^{+/+}$ mice. The exact mechanism by which Nck2 regulates hepatic insulin signaling and glucose homeostasis still remains to be determined, but ourpreliminary data strongly suggestan Nck2 hepatic independent function in the regulation of these processes. In conclusion, our results reveal that in contrast to Nck1,which negatively regulates hepatic insulin signaling, the Nck2 adaptor protein is required to promote hepatic insulin signaling and glucose homeostasis in mice.Funded by *CIHR and CDA*.

Biography

Louise Larose has obtained her Ph.D. in Pharmacology from the University of Montreal in 1992 and completed her postdoctoral training at the Samuel Lunenfeld Research Institute in Toronto in 1995. As an Associate Professor from McGill University in Montreal, she has received the prestigious Chercheur National award from the FRSQ. Her work on the role of the adaptor proteins Nck in molecular mechanisms regulating plasma membrane receptor tyrosine kinases signaling and more recently the unfolded protein response has been published in reputed journals. She is serving as editorial board member, as well as ad hoc reviewer for important journals and panel members of several Canadian funding agencies.

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