Skeletal Muscle H2O2 and Insulin Sensitivity

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Reactive oxygen species (ROS) are thought to contribute to the progression of various human diseases. In type 2 diabetes, ROS are generated by mitochondria, as a by-product of oxidative phosphorylation and as a consequence of inflammation. There is direct evidence for ROS serving to suppress the insulin response and contribute to the development of insulin resistance, a key pathological feature of type 2 diabetes. Paradoxically, ROS generated by NADP(H) oxidases at the plasma membrane and endomembranes may also be required for normal intracellular signaling. A wide variety of physiological stimuli including growth factors, cytokines and hormones such as insulin promote the generation of ROS for the coordinated inactivation of protein tyrosine phosphatases (PTPs) and the promotion of tyrosine phosphorylation, as well as phosphatidylinositol 3-kinase and mitogen-activated protein kinase signaling. Thus, ROS have the potential to both promote and attenuate the insulin response. Our recently published studies (Loh *et al.*, 2009) have focused on the capacity of ROS to promote muscle insulin sensitivity through the inactivation of the PTP superfamily member PTEN, a lipid phosphatase that terminates signals generated by phosphatidylinositol-3-kinase.

Loh, K., Deng, H., Fukushima, A., Cai, X., Boivin, B., Galic, S., Bruce, C., Shields, B.J., Skiba B., Ooms L., Stepto, N., Wu, B., Mitchell, C.A., Tonks, N.K., Watt, M.J., Febbraio, M.A., Crack, P.J., Andrikopoulos, S., & Tiganis, T. (2009) Reactive oxygen species enhance insulin sensitivity. *Cell Metabolism* **10,** 260-272.