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Type II Diabetes – A Disease of Unregulated Calcium?

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decreased while that of negative regulators namely, KLF2, GATA2, miR20a, miR27a, miR27b, miR128, miR130a, miR130b, miR182 and miR548 increased with vitexin treatment. These miRNAs are also involved in modulation of ROS. This Effect was mediated by activation of AMPK pathway via activation of LepR and additionally by inhibiting ROS. Thus, our results showed that vitexin regulates PPARγ, and inhibits adipogenesis of hMSCs at an early stage of adipogenesis.

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Type II Diabetes – A Disease of Unregulated Calcium?

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The plasma membrane calcium ATPase (PMCA) is a high affinity ion transporter that pumps Ca^{2+} out of cells to maintain optimal intracellular Ca^{2+} levels essential for cell function. Previous studies from our laboratory have shown the PMCA to be uniquely sensitive to oxidative stress. Exposure to reactive oxygen species (ROS) of physiological relevance caused dramatic inactivation, aggregation, and proteolytic degradation of the protein. Type 2 diabetes, an extremely prevalent metabolic pathophysiological condition is associated with oxidative stress. Cellular damage caused by ROS exacerbates diabetes and paves the way for the development of other pathological conditions such as cardiovascular disease and neurodegenerative disorders. There is a significant body of literature outlining mechanisms underlying the influx of Ca^{2+} through calcium channels, critical for insulin release by the pancreatic beta cells (PBCs). However, the mechanisms that remove excess intracellular Ca^{2+} and bring it back to baseline levels have not been well studied. The goal of the current research was to determine the effects of oxidative stress on the PMCA in PBCs. Cultured cells were treated with 1- 200 μM of H_2O_2 for 24 hours. PMCA activity was measured by monitoring Ca^{2+} - dependent ATP hydrolysis and PMCA protein levels were determined by immunoblotting. Exposure of cells to H_2O_2 caused a biphasic effect on PMCA activity with a significant stimulation observed at low concentrations of H_2O_2 and inactivation observed at high concentrations. Live cell Ca^{2+} imaging showed a significant increase in intracellular Ca^{2+} levels upon exposure to H_2O_2. Immunoblot analyses showed evidence of PMCA aggregation and fragmentation suggesting structural changes in PMCA. These results indicate a significant impact of oxidative stress on the Ca^{2+} clearance machinery of PBCs establishing a direct link between PMCA and the pathogenesis of diabetes, which can be targeted for therapeutic interventions in the future.

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Exploring the role of compartmentalized H_2O_2 redox signaling in skeletal muscle stress-adaptations

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H_2O_2 is emerging as a diffusible mediator of reversible protein redox modifications to transduce signals in specific subcellular locations. Here, we leveraged state-of-the-art redox tools in skeletal muscle to study the cytosolic and mitochondrial Peroxiredoxins (Prdx) catalyzing the removal and hence diffusion radius of H_2O_2 signaling. Using contraction-mimicking electrical stimulation in C2C12 myotubes, we observed cytosolic oxidation-dependent dimerization of Prdx2, but not of mitochondrial Prdx3, consistent with cytosolic but not mitochondrial H_2O_2 accumulation during muscle contractions. In contrast, mitochondrial H_2O_2 measured using transfected H_2O_2 biosensors increased 4h into recovery after treadmill running in mice, concurrent with reduced muscle protein content of Prdx2 and Prdx3, suggesting that acute exercise increases the oxidation and turnover of Prdx isoforms in both compartments. Total Prdx2 and Prdx3 content increased in mouse muscle with exercise training in a PGC1α-dependent manner and the exercise-training response was reduced in elderly humans. Artificial chemogenetic production of cytosolic H_2O_2 promoted cytosolic Prdx2 dimerization at low H_2O_2 induction rates, whereas mitochondrial Prdx3 dimerization and hyperoxidation was observed at higher cytosolic H_2O_2 induction rates. Overall, we propose that Prdxs determine the compartmentalization and specificity of H_2O_2 signaling. Breakdown of this compartmentalization by increased H_2O_2 production or decreased Prdx isoform expression with aging or physical inactivity may contribute to skeletal muscle dysfunction. We are currently testing this hypothesis in-depth using transgenic drosophila and mouse models.

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Distinct metabolic responses of airway epithelial cells exposed to myeloperoxidase-derived oxidants

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