



A NUCLEAR LOCALIZATION SWITCHABLE DEVICE REVEALS A REGULATORY NETWORK

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Forkhead transcription factors (FOXOs) modulate many cellular processes such as the cell cycle, oxidative stress resistance, and aging (Greer, E, et al. (2005) *Oncogene*, 24, 7410). Insulin/Akt activation directs phosphorylation and cytoplasmic sequestration of FOXO away from target genes and serves as an endpoint of a complex cellular system. We implemented a spatially controlled growth switch using fluorescent FOXO nucleo-cytoplasmic localization to elucidate the Akt signaling network. Using a human genome siRNA library in a microscopy assay, we identified nuclear export factors, mitochondrial components, as well as complexes, such as the proteasome, that were not previously implicated in FOXO localization. Elucidation of mitochondrial factors reveals that loss of uncoupling protein 5 (UCP5) modifies ATP production and increases free radicals. Cellular mechanisms compensate by up-regulation of superoxide dismutase and another uncoupler, UCP3. Up-regulation of UCP3 ultimately decreases the mitochondrial membrane potential. These results entail a switch from glucose metabolism to β -oxidation and protection against fat-induced insulin resistance, a hallmark of obesity and type II diabetes (Choi, C, et al. (2007) *J Clin Invest*, 117, 1995). Taken together, these results demonstrate the value of combining a synthetic mammalian switch device and whole genome inspection to unravel the complexity of a disease process.

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