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PGC-1α Overexpression Improves Angiogenic Signaling Potential of Skeletal Muscle-derived Extracellular Vesicles

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PURPOSE: Skeletal muscle capillary densities are proportional to muscle fiber mitochondrial contents and oxidative capacity. Muscle cells secrete numerous factors that regulate neighboring capillary endothelial cells (EC), including extracellular vesicles (SkM-EV). Peroxisome proliferator-activated receptor-gamma coactivator-1alpha (PGC-1α) is a key regulator of mitochondrial biogenesis and the oxidative phenotype in skeletal muscle and is a molecular driver of adaptations to exercise. Skeletal muscle PGC-1α regulates secretion of multiple angiogenic factors, but it is unknown whether PGC-1α regulates the angiogenic signaling potential of SkM-EVs. **METHODS**: PGC-1α was overexpressed via adenovirus in primary human myotubes. EVs were collected from PGC-1α myotubes (PGC1-EV) as well as from myotubes treated with a GFP adenoviral control (GFP-EV) and from untreated myotubes (CON-EV). Human umbilical vein endothelial cells (HUVEC) were treated with EVs (10 μg/ml) and *in vitro* angiogenic responses were analyzed. To determine if PGC-EVs are protective against oxidative stress, HUVECs were treated with 200 μM H_2O_2 following EV treatments *in vitro* angiogenic responses were analyzed. Significance: $P \leq 0.05$. **RESULTS**: PGC-EV treatment of cultured human umbilical vein endothelial cells (HUVEC) increased HUVEC proliferation (+36.6%), tube formation (length: +28.1%; number: +25.7%), cellular viability (+52.9%), and reduced reactive oxygen species levels (-41%) compared to GFP-EV. Additionally, PGC-EV treatment improved tube formation (length: +52.8%; number: +57%) and reduced cellular senescence (-30.1%) following acute oxidative stress compared to GFP-EV treatment. **CONCLUSIONS**: This report demonstrates that overexpression of PGC-1α in human myotubes increases the angiogenic potential of skeletal muscle EVs. These angiogenic benefits coincided with greater protection against H_2O_2 induced reductions in tube formation and increases in cellular senescence. Increases in PGC-1α expression in skeletal muscle may prompt the release of SkM-EVs that support vascular redox homeostasis and angiogenesis.