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Research Category

Basic Science

Abstract Title

AMPK-dependent extracellular vesicle release from contracting muscle promotes metabolic adaptations in recipient cells.

Authors

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Background

Chronic skeletal muscle contractile activity stimulates mitochondrial biogenesis and systemic metabolic adaptations, through the activation of several signalling kinases, including AMP-activated protein kinase (AMPK). Contractile activity also releases extracellular vesicles (EVs), nanoparticles that carry biological cargo and can alter recipient-cell function. We previously showed that EVs released from muscle after contraction increase mitochondrial biogenesis in recipient cells.

Objective

The signalling pathways controlling contraction-induced EV release, and the metabolic effects of these EVs remain unclear. We hypothesised that acute contraction-mediated EV release is AMPK-dependent, and that these EVs exert pro-metabolic effects in recipient cells.

Methods

Differentiated murine myotubes were pretreated with vehicle (DMSO), or AMPK-inhibitors (Compound C [10 μ M] or SBI-0206965 [10 μ M]), then subjected to electrical pulse stimulation (STIM; 1 Hz, 14 V, 2 ms, 3

h) or control conditions. Conditioned media was collected, and EVs isolated using differential ultracentrifugation or size-exclusion chromatography. EV size and concentration were quantified by tunable resistive pulse sensing; EV protein marker expression, and AMPK inhibition was confirmed by immunoblotting. Recipient myotubes were treated with control or STIM-EVs (100-1000 EVs/cell) for 24 h, after which oxygen consumption rates (OCR) were measured. Data were analysed using paired t-tests.

Results

STIM increased EV concentration 1.6-fold versus control ($p=0.017$, $n=3$). AMPK inhibition with Compound C decreased STIM-EV release by 33% ($p=0.059$, $n=3$), while SBI-0206965 reduced basal EV release by 45% ($p=0.027$, $n=3$). Low-dose STIM-EVs (100 EVs/cell) increased maximal OCR by 9% in recipient myotubes ($p=0.040$, $n=4$); higher doses had no effect.

Conclusion

Acute electrical stimulation of myotubes triggers AMPK-dependent EV release. STIM-EVs enhance maximal respiration in recipient cells at low doses, supporting a role for contraction-induced EVs in pro-metabolic intercellular signalling. These findings provide a putative mechanistic link between muscle activity and systemic metabolic adaptation that warrants further investigation in vivo, and in the context of pediatric metabolic health such as diabetes.