Paper ID: 59014
oral

IAF/IAA SPACE LIFE SCIENCES SYMPOSIUM (A1)
Biology in Space (8)

Author: Prof. Takeshi Nikawa
Tokushima University, Japan, nikawa2001@gmail.com

# MOLECULAR MECHANISM OF MICROGRAVITY-MEDIATED MUSCLE ATROPHY

**Abstract**

Skeletal muscles are vulnerable to rapid and marked atrophy under unloading conditions, such as spaceflight and bedrest. It is important for development of countermeasures to elucidate the mechanisms of unloading-mediated muscle atrophy. We previously demonstrated that elevated ubiquitin ligase casitas B-lineage lymphoma-b (Cbl-b) and reactive oxygen species (ROS) resulted in the loss of muscle volume. However, the pathological association of reactive oxygen ROS production with unloading-mediated muscle atrophy still remains unknown. Here, we showed that the ROS-mediated signal transduction caused by microgravity or its simulation contributes to Cbl-b expression. In L6 myotubes, the assessment of redox status revealed that oxidized glutathione was increased under microgravity conditions, and simulated microgravity caused a burst of ROS, implicating ROS as a critical upstream mediator linking to downstream atrophic signaling. ROS generation activated the ERK1/2 early-growth response protein (Egr)1/2-Cbl-b signaling pathway, an established contributing pathway to muscle volume loss. Interestingly, antioxidant treatments such as N-acetylcysteine and TEMPOL, but not catalase, blocked the clinorotation-mediated activation of ERK1/2. The increased ROS induced transcriptional activity of Egr1 and/or Egr2 to stimulate Cbl-b expression through the ERK1/2 pathway in L6 myoblasts, since treatment with Egr1/2 siRNA and an ERK1/2 inhibitor significantly suppressed clinorotation-induced Cbl-b and Egr expression, respectively. Promoter and gel mobility shift assays revealed that Cbl-b was upregulated via an Egr consensus oxidative responsive element at -110 to -60 bp of the Cbl-b promoter. Together, this indicates that under microgravity conditions, elevated ROS may be a crucial mechanotransducer in skeletal muscle cells, regulating muscle mass through Cbl-b expression activated by the ERK-Egr signaling pathway.