ACTIVATION OF THE UBIQUITIN-PROTEASOME SYSTEM IN MODELS OF MUSCLE WASTING.

JOSEPH J. OLEYNEK, Daniel B. Rouillard, , James P. O'Malley, Chikwendu Ibebunjo, Xiao-Ning Wang, Robert Layfield* and Roger J. Hill. Department of Cardiovascular and Metabolic Diseases, Pfizer Global Research & Development, Groton, CT, USA, and *Queens Medical Center, University of Nottingham, England.

Activation of the ubiquitin-proteasome system (UPS) is a fundamental step in the breakdown of skeletal muscle proteins. The accumulation of poly ubiquitinated proteins (poly Ub) is a direct result of the activation of the UPS. In wasting skeletal muscle, two newly discovered, muscle-specific E3 ubiquitin ligases: muscle ring finger (MuRF-1) and muscle atrophy F-box (MAFbx), have been shown to be markedly upregulated, implying that increases in poly Ub in such tissue are, at least in part, a result of the activation of these ligases. In the present study, we examined levels of MAFbx (Western blotting) and poly Ub (electrochemiluminescence) in skeletal muscle extracts from acute wasting models. Rats subjected to each model exhibited a significant loss of muscle mass from individual muscles. In gastrocnemius muscle from tumor-bearing rats, poly Ub was elevated (255% of control) 6 days after peritoneal inoculation of ascites tumor cells. Poly Ub was also markedly elevated (206% at day 28 vs. day 0) in tibialis muscle from cast-immobilized rats. In denervated muscle, poly Ub was elevated in both extensor digitorum longus (212%) and soleus (178%) within 7 days post denervation. MAFbx protein expression is also elevated in each wasting model. These data provide additional evidence of the importance of the UPS in divergent models of acute muscle wasting, and lead us to propose that the UPS plays a pivotal role in these conditions