UBE2L3, a Partner of MuRF1/TRIM63, Is Involved in the Degradation of Myofibrillar Actin and Myosin

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Abstract: The ubiquitin proteasome system (UPS) is the main player of skeletal muscle wasting, a common characteristic of many diseases (cancer, sepsis, heart failure, kidney diseases, etc.) that negatively impacts treatment and life prognosis. Within the UPS, the E3 ligase MuRF1/TRIM63 targets for degradation several myofibrillar proteins, including the main contractile proteins alpha-actin and myosin heavy chain (MHC) [1]. We previously identified five E2 ubiquitin-conjugating enzymes interacting with MuRF1, including UBE2L3/UbcH7, that exhibited a high affinity for MuRF1 (KD = 50 nM) [2]. Here, we report a main effect of UBE2L3 on alpha-actin and MHC degradation in catabolic C2C12 myotubes. Consistently UBE2L3 knockdown in Tibialis anterior induced hypertrophy in dexamethasone (Dex)-treated mice, whereas overexpression worsened the muscle atrophy of Dex-treated mice. Using combined interactomic approaches, we also characterized the interactions between MuRF1 and its substrates alpha-actin and MHC and found that MuRF1 preferentially binds to filamentous F-actin (KD = 46.7 nM) over monomeric G-actin (KD = 450 nM). By contrast with actin that did not alter MuRF1–UBE2L3 affinity, binding of MHC to MuRF1 (KD = 8 nM) impeded UBE2L3 binding, suggesting that differential interactions prevail with MuRF1 depending on both the substrate and the E2. Our data suggest that UBE2L3 regulates contractile proteins levels and skeletal muscle atrophy.

[1] Peris-Moreno, D.; Taillandier, D.; Polge, C. MuRF1/TRIM63, Master Regulator of Muscle Mass. Int. J. Mol. Sci. 2020, 21, 6663.
[2] Polge, C.; Cabantous, S.; Deval, C.; Claustre, A.; Hauvette, A.; Bouchenot, C.; Aniort, J.; Béchet, D.; Combaret, L.; Attaix, D.; et al. A Muscle-Specific MuRF1-E2 Network Requires Stabilization of MuRF1-E2 Complexes by Telethonin, a Newly Identified Substrate. J. Cachexia Sarcopenia Muscle 2018, 9, 129–145.

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