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A MUSCLE-SPECIFIC MURF1-E2 NETWORK REQUIRES STABILIZATION OF MURF1-E2 COMPLEXES BY TELETHONIN, A NEWLY IDENTIFIED SUBSTRATE

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Muscle wasting is observed in the course of many diseases and also during physiological conditions (disuse, aging). Skeletal muscle mass is largely controlled by the ubiquitin-proteasome system and thus by the ubiquitinating enzymes (E2s and E3s) that target substrates for subsequent degradation. MuRF1 is the only E3 ubiquitin ligase known to target contractile proteins (α-actin, myosins) during catabolic situations (1,2). MuRF1 knock-out partially protected skeletal muscles from atrophy in denervated or immobilized animals (3) MuRF1 is therefore a putative target for preventing muscle wasting. However, MuRF1 depends on E2 ubiquitin conjugating enzymes for ubiquitin chain formation on the substrates.
We focused on 14 E2 enzymes that are either expressed in skeletal muscle or up-regulated during atrophying conditions (4). In this work, we demonstrated that only highly sensitive and complementary interactomic approaches (Surface Plasmon Resonance, Yeast three-Hybrid and split-GFP) allowed the identification of MuRF1 E2 partners. Five E2 enzymes physically interacted with MuRF1, namely E2E1, E2G1, E2J1, E2J2 and E2L3. Moreover, we demonstrated that MuRF1-E2E1 and MuRF1-E2J1 interactions are facilitated by telethonin, a newly identified MuRF1 substrate. We next showed that the 5 identified E2s functionally interacted with MuRF1 since, in contrast to the non-interacting E2D2, their co-expression in HEK293T cells with MuRF1 led to increased telethonin degradation. Finally, we showed that telethonin governed the affinity between MuRF1 and E2E1 or E2J1 (5). We are currently studying the capacity of E2-MuRF1 duos to target the main contractile proteins (actin, myosin heavy chains, …) both *in vitro* and *in vivo*.
We report here the first MuRF1-E2s network, which may prove valuable for deciphering the precise mechanisms involved in the atrophying muscle program and for proposing new therapeutical approaches.

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Keywords: E3 ubiquitin ligase, MuRF1, muscle wasting, ubiquitin conjugating enzyme UBE2.