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## Ubiquitinating enzymes as potential therapeutic targets to prevent muscle atrophy – The case of MuRF1/ TRIM63

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Many pathological conditions (cancer, sepsis, heart failure, kidney diseases, etc.) are associated with skeletal muscle wasting which leads to muscle frailty and has detrimental metabolic consequences for muscle and other organs. There is currently no effective treatment to prevent muscle atrophy. Skeletal muscle mass is largely controlled by the ubiquitin-proteasome system (UPS) and thus the ubiquitinating enzymes (E2s and E3s) that target substrates for subsequent degradation. MuRF1/ TRIM63 is the only E3 known to target contractile proteins ( $\alpha$ -actin, myosins, troponin), the most abundant proteins in muscle, during catabolic situation. MuRF1 is therefore a promising candidate for pharmacological targeting to prevent muscle atrophy. As MuRF1 also targets other classes of proteins, it may be wise to inhibit only part of its functions to avoid the side effects of strict inhibition; for example, by preventing it from interacting with some of its partners. A prime candidate could be the E2s enzymes with which MuRF1 interacts. Indeed, MuRF1, as a RING-type E3, is tightly dependent on E2 ubiquitin-conjugating enzymes for ubiquitin chain formation on the substrates.

Our main objective is then to identify the E2s working in concert with MuRF1 to target myofibrillar proteins in atrophying skeletal muscles. Using complementary biochemical and in cellulo approaches, we have identified five E2 enzymes expressed in muscle that interact with MuRF1, namely UBE2E1, UBE2G1, UBE2J1, UBE2J2 and UBE2L3 (among the 14 E2s expressed in muscle). Biochemical characterization suggested that E2/ MuRF1 interactions are weak and/ or transient. Moreover, we have shown that the presence of a substrate (telethonin and actin) allosterically stabilized some MuRF1–E2 pairs, suggesting that a MuRF1/E2 pair may be specialized for dedicated roles during the degradation of skeletal muscle proteins, with each E2 being used by MuRF1 for specific purposes. We are currently studying the residues involved in the MuRF1-E2 interaction that will help in the design of specific inhibitors of these interactions. These inhibitors may prove valuable for deciphering the precise mechanisms involved in the atrophying muscle program and for proposing new therapeutic approaches.