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From Mechanism to Medicine: Deciphering Transcriptomic Landscapes of Muscle Atrophy for Therapeutic Discovery and Resource Building

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Identifying therapeutic targets is a crucial yet challenging step in drug development, requiring a deep understanding of disease mechanisms. Transcriptomic data coupled with sophisticated bioinformatics analysis provides a powerful resource in this context, offering gene expression characterization at tissue-level with bulk RNA sequencing and at cell-type specific resolution through single-cell transcriptomics. Analyzing both data types facilitates the systematic identification of potential therapeutic targets.

Skeletal muscle plays a vital role in maintaining physiological homeostasis but is susceptible to atrophy due to drug side effect, cancer, or aging. For example, high dose or long-term usage of many glucocorticoids (*e.g.*, dexamethasone) induces muscle atrophy. To investigate drug-induced muscle atrophy mechanism, we generated and analyzed time-series bulk and single-nucleus RNA-seq data following dexamethasone treatment in mouse model system. Our findings indicate that early muscle atrophy is driven by MAPK and FoxO signaling, while prolonged exposure disrupts circadian rhythm pathway, eventually impairing muscle regeneration.

Second, for cancer cachexia, a muscle-wasting condition associated with malignancies, we compiled and analyzed more than 100 publicly available bulk and single-cell transcriptomic datasets from lung, colorectal, and pancreatic cancer-derived mouse models. Our integrative analysis revealed that angiogenesis-associated genes were dysregulated over time in cancer cachectic models. As a result, we found Lrg1 derived from aberrant endothelial cells as a potential therapeutic target for muscle atrophy in cancer cachexia.

Finally, to facilitate further research and therapeutic discovery, we are building a comprehensive Muscle Atrophy Atlas by integrating publicly available transcriptomic datasets from aging, cachexia and denervation models. This resource will be made publicly accessible and is expected to serve as a valuable foundation for target discovery in various muscle-wasting conditions.