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Mini Review

Combined Genomic and Proteomic Investigations Find Stimulus-Dependent Molecular Alterations Linked to Various Forms of Skeletal Muscle Atrophy

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Abstract

Skeletal muscle atrophy is a crippling disorder that develops as people age and get sick, but the underlying causes are still not fully understood. Previous research found that similar transcriptional alterations take place in muscle during atrophy brought on by various stressors. However, nothing is known about whether this is accurate at the proteome level. Contrary to this prior paradigm, we discover that diverse atrophic stressors (such as corticosteroids, cancer cachexia, and ageing) cause essentially unique mRNA and protein alterations during mouse muscle atrophy. Furthermore, the transcriptome-proteome gap is pervasive. As a result, atrophy markers (also known as atrogenes) discovered in prior microarray-based research does not show up in proteomics as typically produced by atrophy. As a result, atrophy markers (also known as atrogenes) discovered in prior microarray-based research does not show up in proteomics as typically produced by atrophy (Al Delaimy et al., 2002). Instead, we discover proteins (herein described as "atroproteins") that are specifically controlled by various forms of atrophy, such as the myokine CCN1/Cyr61, which controls myofiber type flipping during sarcopenia. These combined studies show that various catabolic stressors cause muscle atrophy through substantially separate pathways.

INTRODUCTION

Reduced muscle mass and strength are the major effects of skeletal muscle atrophy, a severe condition linked to ageing and many human illnesses. Numerous studies have shown that maintaining skeletal muscle mass and function is beneficial, whereas muscle atrophy worsens disease outcomes and raises mortality. However, there are currently no treatments available in clinics and little understanding of the causes behind muscle atrophy. It is generally known that, at the cellular level, muscle atrophy is largely caused by the shrinkage of muscle fibres, or myofibers, whose size is regulated by the ratio of protein synthesis to protein breakdown (Armitage et al., 1978). A consistent pattern of gene expression is involved in a variety of skeletal muscle atrophy types, according to groundbreaking earlier research. Particularly, it has been recognised that a few ubiquitin ligases' transcriptional induction is a typical response to a variety of skeletal muscle atrophy brought on by various stimuli, including cancer-associated cachexia, starvation-induced atrophy, denervation, diabetes, kidney failure, and infections (Asimus et al., 2008). These investigations have specifically shown that the autophagy-lysosome and ubiquitin-proteasome systems play a major role in the protein degradation that leads to myofiber atrophy (Armstrong et al., 1998). A number of E3 ubiquitin ligases, namely transcriptional overexpression of Fbxo32 (atrogin-1/MAFbx), Trim63 (MuRF1), Fbxo30 (MUSA), and Fbxo21 (SMART), occur in atrophy and are in charge of poly-ubiquitin tagging and proteasomal destruction of target proteins during muscle atrophy. This area of research has been significantly impacted by the identification of a common transcriptional programme that is engaged in a variety of muscle atrophy types, which has given rise to the theory those anti-atrophy interventions, may be broadly applicable to treat muscle atrophy brought on by a variety of stimuli (Bendayan et al., 1990). Nevertheless, this commendable early research relied on gene expression analysis using microarrays, which has technical limitations in

comparison to modern RNA sequencing (RNA-seq) methods, including a reduced coverage and a smaller quantitative range of gene expression change detection. Recently, new understanding of the transcriptional alterations related to atrophy and muscle homeostasis has been gained by using RNA-seq to analyse muscle atrophy (Benowitz 1990). Muscle atrophy is characterised by extensive proteome remodelling as a result of changes in protein production and degradation, in addition to alterations in gene expression. Only a small number of studies, some of which have limited proteome coverage due to technological limitations and/or concentrate on a specific kind of muscle atrophy, have used proteomics to analyse muscle atrophy (Benowitz 1996). Therefore, an integrated cross-comparison of various kinds of muscle atrophy is lacking, despite the fact that these studies have shed fresh light on the proteome alterations connected to several types of muscle atrophy. Here, we have employed quantitative mass spectrometry and RNA-seq to identify the molecular alterations that take place in mouse skeletal muscle during ageing, cancer cachexia, and dexamethasone-induced atrophy (Novotny et al., 1999). With a 13,000 mRNA overlap, our deep multi-omics method identified over 15,000 distinct mRNAs for each mode and 5,000 unique proteins for each mode (Armstrong et al., 1998).

We discover a remarkable diversity in the mRNA and protein changes induced by different atrophic stimuli, particularly at the proteome level, and a disconnect between transcriptional and proteomic changes, which runs counter to the model that claims a common molecular signature underlies atrophy induced by different stimuli (Thorgeirsson et al., 2008). Furthermore, our proteomic analyses do not show that the majority of the common markers first discovered in microarray studies and generally referred to as biomarkers of atrophy are the most pertinently related with all forms of atrophy. Based on this, our integrated studies suggest that various catabolic stressors can cause muscle atrophy by altering a variety of proteins (Hawkins et al., 2004). These combined integrated multi-omics offer a framework for comprehending the specificity of muscle atrophy brought on by various stressors and offer possible targets for preventing muscle atrophy. We show that Cyr61, identified in our research as an atroprotein linked to ageing, controls myofiber type switching that happens concurrently with muscle atrophy with age. We suggest that these combined studies and datasets are a resource that might be used to create treatments specific to certain forms of muscle atrophy (Cogo et al., 2008).

DISCUSSION

Debilitating skeletal muscle atrophy is a characteristic of several human disorders. Previous investigations have identified a similar collection of genes (atrogenes) that are altered during muscle atrophy in a variety of illness scenarios, including denervation, diabetes, renal failure, cancer-associated cachexia, starvation-induced atrophy, and infections. The identification of several muscle atrophy mediators was made possible by the development of such a molecular signature of muscle atrophy (Yildiz 2004). The ablation of genetic targets discovered to mediate muscle atrophy, such as Fbxo32 (MAFbx/atrogin-1) and Trim63 (MuRF1), however, does not effectively prevent age-associated muscle atrophy and actually compromises muscle function. However, age-induced muscle atrophy (sarcopenia) was not included in these earlier studies. Additionally, the study of proteome alterations has largely gone neglected (Brunnemann et al., 1996). Here, we used combined deep genomic and proteomic investigations to quantify the abundance of more than 15,000 mRNAs and 5,000 proteins under each circumstance. We have determined that different muscle atrophic stressors, such as glucocorticoids (dexamethasone), cancer cachexia, and ageing, produce essentially diverse molecular alterations in muscle on the basis of this thorough genomic and proteomic profiling. In general, compared to ageing, acute types of muscle atrophy brought on by dexamethasone and LLC cancer cachexia overlap more (Campain 2004). For instance, dexamethasone and LLC increase the levels of the mRNAs Trim63 and Fbxo32 in muscle, but not with age. Additionally, we offer proof of deteriorating protein quality control that is specific to ageing. Overall, this suggests that there is a great deal of variation in the genesis and response to atrophic stimuli, and that particularly sarcopenia must be treated differently. Overall, this study provides a comprehensive framework for understanding stimulus-specific muscle atrophy and shows that, in contrast to a prior model, myofiber atrophies with striking clinical similarity may be distinguished molecularly by stimulus-specific protein alterations. As a result, we believe that the datasets from this work may assist focus treatment efforts on creating therapies for stimulus-specific atrophies. With regard to myofiber atrophy brought on by dexamethasone, cancer cachexia, and ageing in particular, the proteomic surveys produced here offer a resource for shortlisting potential protein atrophy indicators that may be experimentally evaluated. We believe that therapeutically focusing on a few of these atroproteins might eventually lead to effective therapies to treat atrophy in various disease contexts.

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