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MINI-REVIEW

Potential of synergist ablation to study mechanisms of skeletal muscle hypertrophy in rodent disease models

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Abstract

Synergist ablation (SA) is a well-established model of mechanical overload-induced hypertrophy in rodents, commonly used to infer skeletal muscle adaptation to resistance training in humans. Given the critical role of skeletal muscle atrophy in chronic conditions such as neuromuscular, metabolic, and cardiopulmonary disorders, SA represents a promising preclinical tool to study muscle hypertrophy mechanisms in pathological states. However, although extensively characterized in healthy animals, the potential applications of SA in disease models remain largely overlooked. This Mini-Review summarizes existing studies employing SA in rodent disease models, highlighting the diverse hypertrophic responses observed across conditions, including Duchenne muscular dystrophy, obesity, diabetes, cancer cachexia, and chronic kidney disease. Although hypertrophy gains are generally attenuated in diseased animals compared to healthy controls, SA-induced overload provides valuable insights into disease-specific regulatory mechanisms, including alterations in intracellular signaling, fiber type transitions, and disease phenotype. We also discuss the strengths and limitations of SA as a preclinical model for resistance training in disease contexts and propose its broader adoption for mechanistic investigations into skeletal muscle plasticity under pathological conditions.

cancer cachexia; exercise; metabolic disorders; neuromuscular disorders; resistance training

INTRODUCTION

Recently, a series of excellent reviews providing a comprehensive overview of the synergist ablation (SA) model were published in the *American Journal of Physiology–Cell Physiology* (1–3). SA typically involves the total or partial removal of the gastrocnemius and/or soleus muscles, thereby placing a mechanical overload on the remaining synergist, the plantaris muscle. This approach serves as a well-characterized and highly reproducible model of hypertrophy in rodents, mimicking the effects of human resistance training (RT). The authors should be commended for extensively discussing this topic, highlighting discoveries from this model, their translation to humans, and key methodological aspects.

With this Mini-Review article, summarized in Fig. 1, we aim to explore the potential of SA in rodent disease models, a largely overlooked application of SA that has not been covered by these previous articles.

RATIONALE FOR THE USE OF SA IN DISEASE RESEARCH

Skeletal muscle atrophy is linked to an increased risk of mortality in many chronic cardiopulmonary, metabolic, and neuromuscular disorders (4). Although exercise is effective in inducing muscle hypertrophy for these conditions (5, 6) and RT is the preferred approach, RT remains often underutilized in patient care because of the complexities of the exercise regime and concerns of exacerbating the pathology. That being said, the health benefits of RT in the context of disease have gained mounting consideration in the past two decades (7, 8). Although the mechanisms of skeletal muscle hypertrophy are relatively well known in healthy individuals (9), these may vary and remain largely unexplored in diseased patients.

Organizing RT studies with muscle biopsies in affected patients is challenging, whereas animal models represent an optimal platform to test mechanistic hypotheses and control

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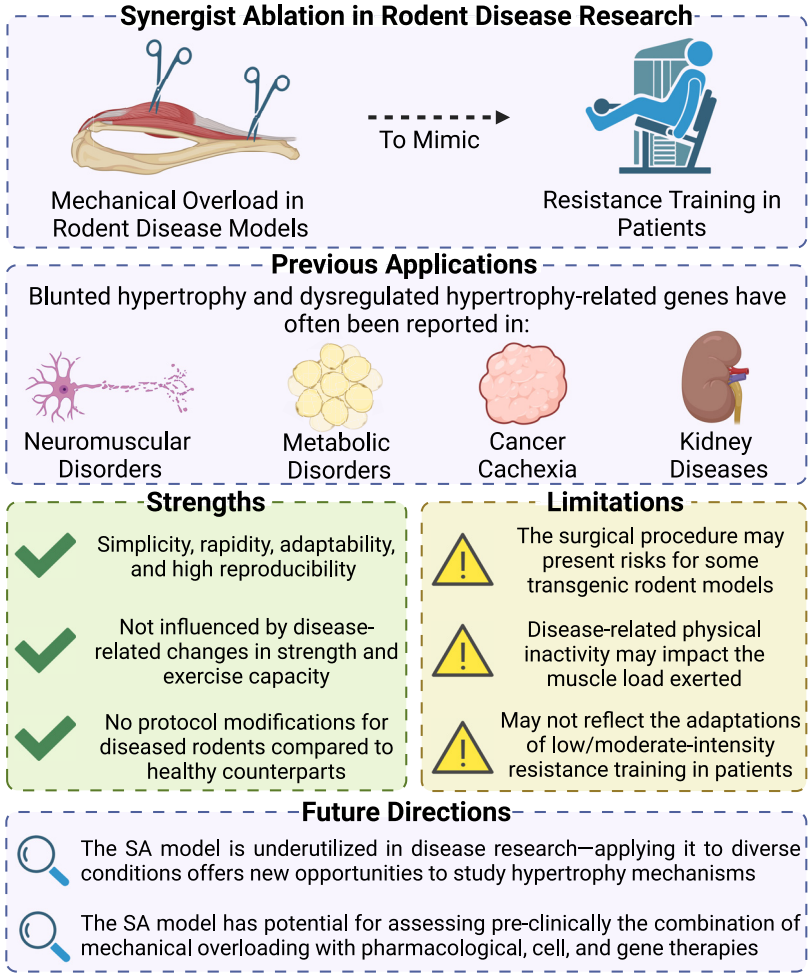

Figure 1. A summary of the previous applications, strengths, limitations, and future directions for the use of synergist ablation (SA) in the context of rodent disease models. Figure created in BioRender.

for multiple variables simultaneously. We contend that SA represents a viable approach to test RT efficacy preclinically and study the cellular and molecular mechanisms by which muscle overloading mediates muscle hypertrophy in disease-specific animal models.

PREVIOUS APPLICATIONS OF SA IN RODENT MODELS OF DISEASE

To illustrate the previous applications of SA in rodent models of disease, we performed a literature search in PubMed using the terms "mechanical overload," "synergist ablation," or "muscle hypertrophy" combined with "neuromuscular disorders," "cardiopulmonary diseases," "metabolic disorders," "cancer cachexia," or "chronic kidney disease." Despite the strong rationale for its adoption, the SA model has seen limited use in rodent disease models, especially in comparison to aerobic exercise interventions (10).

SA-Induced Overload in Neuromuscular Disorders

In neuromuscular disorders like Duchenne muscular dystrophy (DMD), the application of the SA model reveals a muscle response driven by mechanisms distinct from those in healthy muscle (11–15). One to six months of muscle overload induces significant increases in the maximal force in both mild models (*mdx* mice) (12, 14) and severe models (dystrophin-desmin double knockout mice) (15) of DMD. However, these increases are smaller and associated with altered intracellular signaling compared to the hypertrophic response observed in C57 control mice (12). Muscle mass also increases after mechanical overload in the context of DMD (12, 14). This muscle growth is driven by an increased total fiber number per cross section rather than changes in fiber size (14), which instead remains generally stable or shows mild decreases (12–14). In contrast, wild-type mice typically exhibit robust increases in fiber size (13, 16). Regarding the disease phenotype, the results are more heterogeneous and dependent on the duration of the intervention. After 2 wk of overload, the overall profile in *mdx* mice is worsened, with an increased percentage of centrally nucleated and branched fibers (13), highlighting an exacerbation of the characteristic pathology. However, 1-mo overload improves resistance to contraction-induced damage, in the absence of changes in histological markers of muscle damage, compared to *mdx* control mice (14). Another 2-mo SA study reported no changes in centrally nucleated fibers but observed increased fibrosis compared to untreated *mdx* mice (12). Neither short- nor long-term SA depletes satellite cells in the overloaded muscle of diseased mice (13, 14), whereas SA robustly increases satellite cell content in wild-type mice (17). Interestingly, one study reported that mechanical

overload enhanced the efficacy of stem cell transplantation in *mdx* mice (11), suggesting a potential supportive role of overload in regenerative therapies.

SA-Induced Overload in Metabolic Disorders

The SA model was also employed in the context of metabolic disorders. Insulin-resistant obese Zucker rats exhibit a blunted hypertrophic response following 3 and 8 wk of overload, but not after 1 wk, compared to lean control rats (18, 19). This is accompanied by impaired mammalian target of rapamycin (mTOR) activation and altered upstream regulation of the pathway (18, 19). Interestingly, obesity induced by a high-fat diet attenuates muscle growth in response to SA (20) and impairs overload-stimulated increases in muscle glycogen synthesis (21). Similarly, glycative stress induced by injection of advanced glycation end products inhibits protein synthesis and muscle hypertrophy gains, at both whole muscle and single-fiber levels (22). Two studies using a type 1 diabetes model showed a similar magnitude of muscle hypertrophy and force increases between control rats and streptozotocin-induced diabetic rats following SA overload at both 7 and 30 days, both at the onset of the disease (before diabetic myopathy manifestation) (23) and after the establishment of a chronic diabetic condition (24). However, these adaptations are achieved through partially differential regulation of hypertrophy-related genes between wild-type and diabetic groups (23, 24), indicating that different mechanisms may be involved.

SA-Induced Overload in Cancer

The SA model has also been used in the context of skeletal muscle hypertrophy in cancer. Regardless of the cancer type, tumor-bearing rodents retain the capacity to respond to overload during SA periods of 1–6 wk, increasing muscle weight (25–27), improving contractile properties (25), and undergoing a fiber type shift toward a slow phenotype (25, 26). In nonmetastasizing tumors without signs of cancer cachexia, the increase in muscle weight relative to the contralateral sham-surgery limb is similar between tumor-bearing and control mice (25). In contrast, in tumors leading to cancer cachexia, the increase in muscle weight relative to the contralateral sham-surgery limb is lower in tumor-bearing mice than in control mice (26, 27). This blunted hypertrophic response appears to be driven by inactivation of the mTOR complex 1 pathway due to an impaired activation of insulin-like growth factor-1 (IGF-1)-dependent signaling, at least in a cancer cachexia model induced by transplantation of a colon cancer-derived cell line (27).

SA-Induced Overload in Chronic Kidney Diseases

Several studies have investigated the application of SA also in the context of chronic kidney diseases. Considering the resistance to growth hormone (GH)-stimulated IGF-1 expression that develops in uremia, a study explored whether increasing muscle overload, a GH-independent stimulus for local IGF-1 expression, could bypass this defect (28). Employing rats with surgically induced chronic renal failure (CRF), this study showed that overload (2–7 days of SA) is an effective means of stimulating local IGF-1 mRNA expression in the uremic state, while also decreasing myostatin levels (28). Overload also led to similar gains in muscle weight in both CRF and paired control groups, correcting the uremic muscle atrophy (28). Accordingly, data from the same research group support that insulin receptor substrate-1/phosphoinositide 3-kinase/Akt pathway can be fully activated by 7 days of overload in CRF rats, and this is partially mediated by increased signal protein levels and decreased suppressor of cytokine signaling-2 mRNA expression (29). Muscle overload not only increases plantaris weight and reduces muscle proteolysis but also corrects intracellular signals regulating protein and progenitor cell function in a similar mouse model of chronic kidney disease (30). Interestingly, the SA protocols mimicking RT appear to be more effective than aerobic training in the context of kidney diseases, as treadmill running corrects only muscle proteolysis but not protein synthesis or progenitor cell function (30).

Overall, these studies highlight the feasibility and potential of SA to investigate how overload affects skeletal muscle, even with blunted response, in rodents with different underlying pathologies, providing insights for informing patient outcomes following RT.

STRENGTHS AND LIMITATIONS OF SA IN THE CONTEXT OF DISEASE

The SA model offers significant advantages for inducing muscle hypertrophy in rodent disease models. Its simplicity, rapidity, and adaptability make it preferable to other translatable models, reviewed elsewhere (31), that mimic RT in animal models, such as weighted wheel running (32), squat-like exercises (33), and weight pulling (34). These alternative approaches, although potentially more clinically relevant, are complex to implement and may be heavily influenced by disease-related changes in strength and exercise capacity. Moreover, these models have not yet been adapted for use in diseased animals, making the development of appropriate protocols (e.g., adjustments to loads, sets, and recovery times) both labor-intensive and challenging. In contrast, the SA model relies on surgical induction of mechanical overload, requiring no modifications for diseased rodents compared to healthy counterparts. This consistency, coupled with its high reproducibility (1), supports its application across diverse disease models and ensures comparability with existing literature. Although we recognize the value of translatable models, we propose that SA serves as a reliable and efficient first-line approach for studying muscle hypertrophy in disease scenarios.

The SA model, however, does have limitations. First, the invasive nature of the surgical procedure may pose risks for transgenic rodent models with high mortality rates. An additional potential limitation of using the SA model in rodents with an underlying pathology is the disease-related reduction in physical activity levels. For example, tumor-bearing mice with cancer cachexia are less active in home cages compared to non-tumor-bearing mice (35), which may impact the muscle load exerted after SA surgery and comparability of the results with the control group. On the other hand, this can also be considered a strength of the SA model, as soleus and/or gastrocnemius removal largely increases the postural demand on the plantaris, ensuring overload even with minimal activity. Furthermore, the supraphysiological muscle growth induced

by SA (2, 3) may not always reflect adaptations seen with low- or moderate-intensity RT, typically recommended for patients. For instance, the very high-intensity overloading stimulus induced by SA could potentially comprise some aspects of the disease phenotype in DMD, as presented above, unlike in humans, where RT is considered safe (6). However, it must be considered that the kinetics of regeneration differ significantly between rodents and humans (36), and recently introduced modifications in the surgical approach involving milder overload (37, 38) may mitigate this issue. Nevertheless, these disparities highlight the need for caution when extrapolating SA findings to clinical scenarios.

CONCLUSIONS AND FUTURE DIRECTIONS

Molecular and cellular mechanisms of the hypertrophic responses may vary across different diseases, potentially leading to blunted muscle adaptation. We propose that SA can be a widely adopted approach to mimic RT in rodent disease models because of superior applicability, ease of adaptation, and high reproducibility. In addition, this model has the potential to preclinically assess the combination of mechanical overloading with pharmacological as well as cell and gene therapies to ultimately rescue muscle atrophy and weakness associated with chronic diseases.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

F.S. prepared figure; F.S. drafted manuscript; F.S., C.S.F., M.V.N., L.L.R., and F.D.P. edited and revised manuscript; F.S., C.S.F., M.V.N., L.L.R., and F.D.P. approved final version of manuscript.

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