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Targeting myostatin in cancer cachexia: Exploring the potential of MSTN gene therapy

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AUTHOR BIO

Krish Penumarthi is a sophomore at Carroll High School in Southlake, Texas, with a passion for researching musculoskeletal diseases. His interest began through weightlifting and AP Biology, and he now studies in medical-related classes in his district's pre-med program. Krish hopes to become a sports medicine physician.

ABSTRACT

Cancer cachexia is a debilitating syndrome associated with advanced-stage cancer and marked by involuntary weight and muscle loss. One of the most promising targets for intervention is myostatin, a protein known for suppressing muscle growth. This paper investigates the role of myostatin in cancer-induced muscle wasting and explores MSTN gene therapy as a potential treatment. A systematic review of 20 peer-reviewed articles published between 2018 and 2025 was conducted using PubMed, ScienceDirect, and Google Scholar. Results from animal models showed that myostatin inhibition improved muscle mass, preserved strength, and even reduced tumor progression. In addition, gene therapy targeting the MSTN gene demonstrated potential in halting muscle atrophy. However, human clinical trials testing agents such as LY2495655 and STM 434 reported mixed efficacy and adverse effects, including fatigue, anorexia, and bleeding complications. These inconsistencies between preclinical and clinical outcomes highlight the need for continued research. With further clinical testing and refinement, MSTN-targeted therapies may provide a new pathway to improve quality of life and prognosis in cancer patients suffering from cachexia.

Keywords*:* *myostatin inhibition, MSTN, gene therapy, cancer, cachexia, muscle wasting, targeted therapy, treatment*

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INTRODUCTION

Cancer, a very broad term for one of the deadliest diseases in history, caused approximately 10 million deaths globally in 2022 alone (World Health Organization, 2024). In general, cancer refers to a group of diseases characterized by uncontrolled cell growth and proliferation, potentially spreading to surrounding tissues and bodily regions through a process known as metastasis (*What Is Cancer? - NCI*, 2021). A common and severe complication of patients with advanced cancers is cachexia, a stage in the disease that contributes to rapid weight loss in both muscle and fat tissue. Cachexia significantly impacts the patient's quality of life and survival outcomes (Ni & Zhang, 2020). With the rise of cancer, understanding cachexia is crucial due to its negative influence on patient prognosis and treatment.

Cachexia is especially evident in those with colorectal and lung cancer, developing in 50%-80% of those diagnosed with advanced stages (Yue et al., 2024). Aside from the development of cachexia, those who are diagnosed with this syndrome typically experience anorexia, insulin resistance, and weight loss (Daley et al., 2025). Currently, interventions for those with cachexia are limited to nutritional counseling, physical activity, and drugs to promote appetite (Kadakia et al., 2023). Given the awareness of this syndrome and the potential effectiveness of treatment, such an intervention would benefit all those suffering from its symptoms. Myostatin inhibition offers an intervention that has yet to be rendered in the clinical setting.

Myostatin, or growth differentiation factor 8 (GDF-8), is a protein responsible for regulating skeletal muscle growth and differentiation (Meloux et al., 2019). Being part of the factor-beta (TGF-β) family, myostatin, when elevated, is associated with significant muscle loss, similar to the symptoms of cancer cachexia patients, due to the protein's active inhibition towards muscle hypertrophy and promotion of muscle degradation pathways (Baig et al., 2022). To combat muscle loss, therapeutically targeting myostatin through inhibition has emerged in recent studies. Within animal models and limited human clinical trials, the blocking of myostatin has demonstrated improved muscle mass and overall strength (Jang et al., 2021).

Gene therapy is an evolving medical practice designed to deliver genetic material directly to the patient on a molecular level to treat or prevent disease. This technique has provided notable clinical success in conditions associated with specific genetic instabilities or cancer (*Gene Therapy*, 2024). Regarding muscular dystrophy, recent research in gene therapies targeting the myostatin (MSTN) gene, responsible for coding myostatin, shows a promising method to mitigate muscle wasting by directly reducing myostatin expression. In cancer patients suffering from cachexia, inhibiting myostatin may lead to reduced weight loss and increased overall strength (Setiawan et al., 2023)

Given the severe implications of cancer cachexia and the possible treatments, comprehensively examining myostatin's role in muscle loss among cancer patients is monumental. Therefore, this paper seeks to address how myostatin contributes to cancer cachexia while serving as a potential target for preventing muscle wasting in cancer patients. Researching the genetic targeting of MSTN and the results

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of myostatin inhibition could significantly advance clinical treatment, ultimately improving the patient's prognosis and quality of life.

METHODOLOGY

A systematic literature review was conducted using PubMed, ScienceDirect, and Google Scholar for reputable sources. The databases were searched using the terms "myostatin inhibition," "cancer cachexia," and "MSTN gene therapy." Only articles written in English and published from 2018 to 2025 were eligible for selection. A total of 86 articles were reviewed, and ultimately 20 of the articles were used for analysis.. The AI tool Elicit was utilized in the introduction and results section to assist with source acquisition and partial synthesis. Additionally, ChatGPT's 4.5 model was used to summarize an abstract for this paper.

RESULTS

Myostatin's contribution to cancer cachexia

Myostatin is deemed an effective negative regulator of skeletal muscle growth. Elevated levels of myostatin are evident in the pathogenesis of muscle wasting observed in cancer cachexia (Setiawan et al., 2023). Highlighted in various studies, overexpression of myostatin leads to muscular atrophy, or the loss of muscle tissue, and its inhibition can reduce muscle wasting (Mitra et al., 2023). For instance, research has identified that tumor-derived factors can further enhance myostatin production, decreasing muscle mass in cancer cachexia patients (Siff et al., 2021). Moreover, data from preclinical models have confirmed that increased myostatin directly correlates with reduced muscle fiber count and size (Baig et al., 2022). Collectively, these findings reinforce the role myostatin plays as an inducer in muscle degradation, particularly in cancer cachexia patients, while demonstrating the protein as a target for future treatment. Preclinical research has shown that myostatin inhibition has the potential to be an effective form of treatment in reducing muscle wasting in cancer cachexia. Initially, animal models such as mice have been experimented with using myostatin inhibitors. For example, MID-35, a peptide inhibitor, and SB-431542, a molecular inhibitor, showed signs of reduced MSTN gene expression (Hanada et al., 2022). Furthermore, in mice with tumors treated with ActRIIB-Fc, a soluble decoy protein, preserved muscle mass was indicated compared to the untreated control groups (Queiroz et al., 2022). Although these results provide promising data, animal trials have reported the negative side effect of increased fatigue, supplementing the reason for limited human trials.

Gene Therapy Targeting MSTN

The MSTN gene, responsible for myostatin production, is being explored through gene therapy to combat muscle loss in cancer cachexia. Animal studies have shown that disabling the MSTN gene can halt muscle wasting and, at times, slow down cancer growth. For example, in experiments with lung cancer-afflicted mice, those receiving myostatin/activin A receptor inhibitors maintained their muscle mass and had reduced tumor sizes compared to untreated mice (Walton et al., 2019). However, applying

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gene therapy in humans presents many hurdles. Concerns regarding potential gene errors, incorrect cell targeting, undesirable immune system response, and the possibility of infection remain significant risk factors (*Gene Therapy*, 2024). These concerns explain why only 22 human trials that have reached phase II or phase III have explored MSTN inhibition (Lee, 2021).

Clinical trials and outcomes

With minimal clinical evidence available, current data on myostatin inhibition in cancer patients have displayed mixed outcomes. For example, a phase II randomized, double-blind, placebo-controlled trial of 125 patients with pancreatic cancer (stage II-IV) evaluated the success of LY2495655, an anti-myostatin antibody, when combined with standard physician-diagnosed chemotherapy. Participants received either 300 mg or 100 mg of LY2495655 combined with standard chemotherapy. Unfortunately, due to an imbalance in death rates between treatment groups, the study was prematurely terminated. Specifically, the hazard ratio for overall survival was 1.70 (90% confidence interval [CI], 1.1–2.7) for the 300 mg group and 1.3 (90% CI, 0.82–2.1) for the 100 mg group compared to placebo. Additionally, LY2495655-treated patients experienced higher rates of anorexia, diarrhea, and fatigue when compared to the placebo counterpart (Golan et al., 2018). Overall, these findings, as opposed to the success of animal models, propose that myostatin inhibition in cancer patients requires managed testing and consideration of potential side effects.

STM 434, a soluble receptor ligand trap that targets the myostatin-related protein activin A, was the subject of another study. A total of 32 patients with advanced solid tumors, including ovarian granulosa cell tumors, were given STM 434 in eight dose groups ranging from 0.25 mg/kg every four weeks to 8 mg/kg every two weeks as part of a first-in-human phase I clinical trial. Fatigue (41%) and mucocutaneous bleeding problems, including gingival bleeding (22%), were the most frequent treatment-related side effects. These may have been triggered by off-target suppression of bone morphogenetic protein 9 (BMP9). Activin A inhibition-related metabolic effects, such as increases in total lean body mass and 6-minute walk test distance, were noted despite the lack of significant clinical responses to STM 434 therapy (Tao et al., 2019).

CONCLUSION

The purpose of this paper was to research how myostatin contributes to muscle wasting in cancer cachexia and to evaluate how the protein plays a role in treatment through MSTN gene therapy. Initial findings concluded that increased myostatin levels are what cause muscle loss, in addition to tumor-derived factors. Preclinical studies using animal models displayed optimistic outcomes such as improved muscle mass and strength, and reduced tumor growth. However, differences in muscle structure between animals and humans require a thorough study before treatment. Human clinical trials displayed inconsistency, such as the negative side effects of myostatin inhibition. Ongoing research and trials are essential to address these challenges before MSTN gene therapy becomes a viable treatment for cancer-related muscle loss.

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To improve future research, clinical trials must focus on addressing limitations by revising patient selections, calculating proper doses, and further investigating the adverse side effects of myostatin inhibition. Further systematic human studies are necessary to determine the crucial implications of MSTN gene therapy, address the current challenges, and identify novel treatment possibilities for muscle wasting syndromes. Ultimately, MSTN gene therapy and myostatin inhibitors are favorable to improving prognosis and overall quality of life in cancer patients suffering from cachexia.

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