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Emerging mechanisms for exercise effects on muscle wasting and anabolic resistance

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Introduction

At the 2018 Annual Meeting of the American College of Sports Medicine, presentations were given by Drs. Nicholas P. Greene, James A. Carson, and James D. Fluckey, at a symposium titled “Emerging Mechanisms for Exercise Effects on Muscle Wasting and Anabolic Resistance”. Inspired by the presentations at this symposium, the following reviews have been crafted to examine the current understanding of muscle diseases characterized by muscle wasting and anabolic resistance, particularly their identification, development, progression, and mitigation. Today, cancer accounts for roughly 1 in every 6 deaths worldwide,[1] and cancer cachexia is directly attributable to up to 40% of cancer-related deaths.[2–5] The review from Dr. Greene's group (Lim et al.) provides an overview of perspectives in cancer cachexia. While the work from Dr. Carson's group (Halle et al.) then expands on concepts in cancer cachexia to examine muscle more specifically and how exercise may serve as a countermeasure to cancer cachexia. Finally, the work from Dr. Fluckey's group (Deaver et al.) assesses the regulation of anabolism with a particular focus on mRNA translation, a critical aspect to the maintenance of skeletal muscle mass. While these reviews are united in their inspiration and in their overarching topic, each review offers a unique perspective, and together represent an exciting overview of the current literature pertaining to skeletal muscle wasting diseases. This editorial provides a brief introduction to each of these reviews.

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Authors’ contributions

All contributing authors are represented in the list of authors appearing on the manuscript, and all authors approve of this manuscript and agree with submission for consideration of publication in Sports Medicine and Health Science.

Conflict of interest

The authors declare to no conflicts of interest that could influence the interpretations of this work.

Development and progression of cancer cachexia: perspectives from bench to bedside

Understanding the development and progression of cancer cachexia continues to be crucial to the development of potential therapies to mitigate the impact of a condition that affects approximately 80% of cancer patients worldwide. Despite the enormous impact of cancer cachexia on patient outcomes, specific mechanisms that drive this wasting disease are not fully understood. In this review, the authors provide an overview of the current understanding of the development and progression of cancer cachexia from not only within skeletal muscle, but from a whole-body perspective that includes pathological changes to the liver, heart, brain, and adipose tissue. This work highlights not only the critical understanding of known alterations to skeletal muscle but also the relative dearth of understanding regarding the role of non-muscle tissue in cancer cachexia. By examining the onset of development of cancer cachexia in multiple tissues and as a function of age, biological sex, and the type of cancer, it may be possible to identify pre-cachectic signatures to aid in the early diagnosis and treatment of cancer cachexia.

Exercise as a therapy for cancer-induced muscle wasting

Utilizing exercise as a therapy to preserve skeletal muscle mass during cancer cachexia has become an increasingly hot topic over the past few years.[2,6–8] Currently, the American Society of Clinical Oncology cannot recommend exercise-based therapies to combat cancer cachexia, citing a lack of clinical trial evidence.[9] However, given the importance of preserving skeletal muscle mass and function during cancer cachexia, exercise continues to hold great promise to mitigate the effects of this wasting disease. The authors highlight the interaction between exercise effects and the progression of cancer cachexia, and how the anti-inflammatory and metabolic adaptations to exercise in skeletal muscle interact with established regulators of cancer-induced muscle wasting. This review stresses the importance of a deep understanding of the mechanisms of pathophysiology in cancer cachexia to aid in establishing exercise dosing regimens to improve skeletal muscle and whole-body health during cancer cachexia.

Regulation of cellular anabolism: by mTOR or how I learned to stop worrying and love translation

Although the precise mechanisms that lead to muscle wasting are not completely understood, there have been several advances in the understanding of cellular metabolic regulation that provide insight into the role of anabolism in the function of normal healthy cells and in disease states characterized by anabolic dysfunction. The mechanistic target of rapamycin (mTOR) has long been the subject of many investigations of cellular anabolism, due in large part to its central role in the integration of many extracellular and intracellular signaling inputs that serve to regulate cellular anabolism. In this review, the authors present a brief review of the complexities of cellular metabolic regulation, with a particular focus on the mechanisms governing mRNA translation initiation. While this review takes a more bottom-up approach to the topic, it provides an interesting overview of the current

understanding of mRNA translation initiation including non-canonical mechanisms that may be of great importance in skeletal muscle during multiple pathologies, including cancer cachexia.

Conclusion

These brief reviews offer a multifaceted view of the current state of research in muscle wasting and anabolic resistance. Each perspective highlights the importance of maintaining skeletal muscle health in the face of wasting diseases, and establish compelling arguments for mechanisms contributing to the onset and progression of skeletal muscle wasting. While these reviews are brief, together they offer an up-to-date account of our understanding of the factors that contribute to the loss of skeletal muscle during conditions including cancer cachexia and anabolic resistance, and how exercise can mitigate some of these detrimental effects.

Submission statement

We confirm that we have given due consideration to the protection of intellectual property associated with this work and there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

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