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Skeletal muscle proteostasis in health and disease states: the role of stable isotopes in contemporary clinical nutrition research

Understanding muscle proteostasis in clinical and nutritional research is necessary to improve the lives of patients who suffer from sarcopenia, chronic diseases, or critical illness; in middle-aged populations who want to age healthily and for athletes for whom physical performance is a professional requisite. Such research - directly in humans - is necessary for both societal and scientific reasons. Indeed, we urgently need improved understanding, and treatments, for the global public health problem that is functional decline in ageing and diseases. Muscle proteostasis differs across species, as a result of distinct evolution and entropic states, resulting in limited trans-species translatability of knowledge. Human research is thus required both to inform the science of human muscle physiology, but also to speed development of interventions to mitigate functional declines.

Key to such understanding is the regulation of muscle protein synthesis; a process which has been long established as driving physiological change in humans i.e. muscle growth and muscle loss, with muscle protein breakdown being adaptive, in turn. Accordingly, measurement of these processes is central to understanding muscle proteostasis. In this special issue of *Clinical Nutrition Experimental*, *Wilkinson* and colleagues take us through a history of stable isotope tracer use, covering 80 years of research and development beginning with the work of *Schoenheimer* and *Rittenberg* in the 1930's. Interestingly, tracer work has recently circled back to the original stable isotope of deuterium oxide (D_2O), with modern techniques now allowing the ability to measure dynamic proteostasis (the major advantage of stable isotope research), over hours, days, weeks and months. Cutting-edge methods in proteostasis and substrate flux are discussed.

Dietary protein ingestion is, in addition to physical activity, the principal environmental determinant of diurnal muscle protein synthesis. *Trommelen et al.* discuss the principles of amino acid bioavailability. They describe differences between protein digestion and amino acid absorption, the need to separate these processes to understand bioavailability, in addition to oral-intravenous dual tracer methods to assess bioavailability. Precisely how amino acid bioavailability drives the whole body anabolic response is addressed by *Wolfe et al.* who covers the rationale for stable isotope techniques to quantify dynamic changes in protein kinetics from basal states. Challenges in interpretation of whole-body data using single isotope techniques are discussed, in addition to methods to overcome these.

Chapple and colleagues move the focus towards the direct muscle relevance of stable isotope techniques, arguing that whole body proteostasis experiments are only the first step towards improving muscle mass outcomes. The case for limb net balance is made for offering the most complete picture in relation to muscle-specific outcomes, using arterio-venous balance methodology and/or

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stable isotope incorporation via muscle biopsy. In keeping with the focus on improving outcomes, *Joanisse et al* highlight the synergistic relationship between exercise and nutrition. While exercise and nutrition are routinely separated when examined academically, managed professionally or prescribed clinically, they are irrevocably link biologically within our patients, rendering any such separation artificial. Muscle protein synthesis responses to protein doses in conjunction with resistance exercise, Omega-3 polyunsaturated fatty acids and creatine are discussed. The role of insulin in the modulation of muscle protein breakdown is also addressed, in keeping with the need to address both aspects of proteostasis.

As editors of this issue of complementary articles from leaders, in the still relatively niche field of clinical experimental stable isotope research, we sincerely hope this collection promotes the varied and insightful value of such research.

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