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The putative role of the Sestrins as leucine sensors in skeletal muscle: a scoping review protocol

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ADMINISTRATIVE INFORMATION

Support - NSERC.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 20 March 2026 and was last updated on 20 March 2026.

INTRODUCTION

Review question / Objective What evidence supports a role for Sestrins as leucine sensors regulating mTORC1 signaling in skeletal muscle across cellular, rodent, and human models?

-Population: Skeletal muscle (cells, tissue, in vitro, rodent, human)

-Concept: Sestrins (SESN1/2/3) as leucine sensors, mTORC1 signaling, amino acid sensing in skeletal muscle

-Context: Nutrient manipulation (leucine, amino acids), physiological stimuli (e.g., fasting, feeding, exercise, immobilization, bedrest).

Background Skeletal muscle mass is dynamically regulated by the intricate balance between muscle protein synthesis and breakdown, with amino acid availability serving as a critical determinant of anabolic signaling. Among amino acids, leucine has emerged as a key regulator of muscle protein synthesis, primarily through its activation of the mechanistic target of rapamycin complex 1 (mTORC1). Leucine-mediated activation of mTORC1 promotes translation initiation and ribosomal biogenesis, thereby supporting muscle maintenance and growth. This process is particularly relevant in contexts such as aging, resistance exercise, and clinical conditions characterized by anabolic resistance.

Despite the well-established role of leucine in stimulating mTORC1 signaling, the molecular mechanisms by which cells sense intracellular leucine availability remain less understood. Early models of amino acid sensing implicated lysosomal machinery, including Rag GTPases and associated regulatory complexes, as central mediators of mTORC1 activation. However, these models did not fully explain how leucine itself is detected at the molecular level.

More recently, members of the Sestrin family of stress-inducible proteins have been proposed as putative intracellular leucine sensors. Sestrins are conserved proteins involved in cellular homeostasis, with established roles in oxidative stress responses, autophagy, and metabolic regulation. Emerging evidence suggests that Sestrin2 can bind leucine directly, thereby modulating its interaction with upstream regulators of mTORC1 signaling, such as the GATOR complex. In this model, leucine binding to Sestrin2 disrupts its inhibitory interaction with GATOR2, ultimately facilitating activation of mTORC1.

Preclinical studies using in vitro and animal models have provided support for this mechanism, demonstrating that Sestrin2 deficiency or mutation alters leucine sensitivity and mTORC1 signaling dynamics. However, the extent to which these findings translate to skeletal muscle physiology, particularly in humans, remains unclear. Furthermore, the relative contribution of Sestrins compared to other proposed leucine-sensing mechanisms continues to be debated.

Given the central importance of leucine in regulating muscle protein synthesis and the growing interest in targeting amino acid sensing pathways for therapeutic and nutritional interventions, there is a need to systematically map the existing evidence on the role of Sestrins as leucine sensors in skeletal muscle. A scoping review is well suited to this objective, as it allows for the identification and characterization of the evidence across diverse study designs and experimental models.

Rationale Although substantial progress has been made in elucidating the role of leucine in activating mTORC1 signaling, the molecular basis of leucine sensing remains relatively underexplored. The identification of Sestrins as potential leucine sensors has generated considerable interest, as it offers a mechanistic link between amino acid availability and intracellular signaling pathways that regulate muscle protein synthesis. However, the evidence supporting this role is heterogeneous, spanning multiple experimental models, methodological approaches, and biological contexts.

To date, no comprehensive synthesis has mapped the extent, range, and nature of the literature specifically examining Sestrins as leucine sensors within skeletal muscle. Existing studies vary widely in terms of experimental model (e.g., cell culture, rodent models, and limited human data), outcome measures (e.g., mTORC1 signaling, molecular interactions, gene expression), and the specific Sestrin isoforms investigated. This heterogeneity presents challenges for drawing definitive conclusions and highlights the need for a structured approach to evidence synthesis.

A scoping review is therefore warranted to systematically identify, categorize, and summarize the available evidence. Unlike systematic reviews focused on narrowly defined questions or effect estimation, this approach is designed to map key concepts, clarify definitions, and identify gaps in knowledge. In the context of Sestrin biology, such an approach will enable the integration of mechanistic and physiological evidence, providing a clearer picture of the proposed role of Sestrins in leucine sensing with respect to skeletal muscle.

The findings of this review will have important implications for both basic and applied research. From a mechanistic perspective, it will help to consolidate the evidence on whether Sestrins function as leucine sensors in skeletal muscle. From an applied standpoint, improved understanding of leucine sensing pathways may inform the development of targeted nutritional or pharmacological strategies to optimize muscle health, particularly in populations affected by anabolic resistance such as older adults or during critical illness. In addition, this review will identify gaps in the current literature, including limitations in translational evidence and inconsistencies across experimental models. These insights will be valuable in guiding future research priorities and refining hypotheses related to amino acid sensing and muscle metabolism.

METHODS

Strategy of data synthesis The data will be synthesized using a descriptive and narrative approach in accordance with established guidance for scoping reviews (e.g., PRISMA-ScR). Given the anticipated heterogeneity in study designs, experimental models (e.g., in vitro, rodent, and human studies), and outcome measures, quantitative synthesis (meta-analysis) will not be performed.

The following electronic databases will be searched: PubMed, Web of Science, Scopus, Embase. All search terms, Boolean strings, and database-specific syntax will be documented. No restrictions will be placed on the date of publication, and English language papers only will be included in the review.

Extracted data will be summarized in tabular form to provide an overview of study characteristics, including study design, model system, skeletal muscle context, and key findings related to Sestrin function and leucine sensing. Studies will be grouped and categorized based on relevant conceptual domains, including: (1) evidence supporting Sestrins as leucine sensors, (2) mechanistic insights into Sestrin-mediated regulation of mTORC1 signaling, and (3) differences across experimental models or physiological conditions.

Key variables and terms of interest for the review may include: species/model, muscle type, stimulus/intervention (e.g., leucine, contraction, fasting, immobilization), Sestrin type (1/2/3), method of quantification (mRNA/protein), key outcomes (e.g., mTORC1 activity, muscle protein synthesis).

A narrative synthesis will accompany the tabulated results, focusing on identifying patterns, consistencies, and discrepancies in the literature. Particular attention will be given to the strength and type of evidence supporting the proposed role of Sestrins in leucine sensing, as well as gaps in knowledge and areas requiring further investigation.

Where appropriate, results will be further stratified by study type (e.g., in vitro vs. in vivo vs. human studies) and methodological approach to highlight differences in evidence generation. The findings will be presented in a manner that maps the current state of the literature and clarifies the extent, range, and nature of research activity in this field.

Eligibility criteria Inclusion: Original studies; Sestrin expression/abundance/function measured in skeletal muscle; Studies assessing leucine exposure OR amino acid signaling OR mTORC1 pathway outcomes

Exclusion: Non-skeletal muscle cell or tissue; Purely descriptive Sestrin papers with no link to nutrient signaling; Non-human/rodent investigations.

Source of evidence screening and selection All records identified through database searching will be exported into a reference management software (e.g., EndNote) for initial organization and removal of duplicate entries. Following de-duplication, records will be imported into Covidence to facilitate the screening and study selection process.

The screening and selection process will be conducted in two stages: (1) title and abstract screening and (2) full-text review. Prior to formal screening, a pilot phase will be conducted on a subset of records to ensure consistency in the interpretation and application of the eligibility criteria across reviewers. The eligibility criteria may be refined iteratively during this process to improve clarity and agreement.

For title and abstract screening, two reviewers will independently assess all records against the predefined inclusion and exclusion criteria. Studies considered potentially relevant by at least one reviewer will be advanced to full-text review. Discrepancies will be resolved through discussion, with consultation from a third reviewer if consensus cannot be reached.

Full-text articles will be retrieved and assessed independently by two reviewers to determine final inclusion. Reasons for exclusion at the full-text stage will be documented and reported. Any disagreements will be resolved through discussion or, where necessary, adjudication by a third reviewer.

The overall study selection process will be documented using a PRISMA-ScR flow diagram, detailing the number of records identified, screened, excluded, and included at each stage of the review.

Data management All records identified through database searching will be exported into a reference management software (e.g., EndNote) for initial organization and duplicate removal. Following de-duplication, records will be imported into Covidence to support the screening and study selection process.

A standardized data charting form will be developed in Microsoft Excel and pilot-tested on a subset of included studies to ensure consistency and completeness. The form will capture key study characteristics, including author(s), year of publication, study design, experimental model (e.g., in vitro, rodent, or human), skeletal muscle context, details of Sestrin-related mechanisms, leucine sensing pathways (including mTORC1 signaling where applicable), and relevant outcomes and findings. The data charting form will be iteratively refined throughout the review process as needed.

Data extraction will be conducted by two reviewers independently for a subset of studies to ensure consistency, with the remaining studies extracted

by one reviewer and verified by a second. Any discrepancies will be resolved through discussion, with involvement of a third reviewer if consensus cannot be reached.

All data will be stored securely within Covidence and on password-protected institutional or cloud-based storage systems accessible only to the review team. Regular backups will be maintained to prevent data loss. Version control will be ensured through dated file naming conventions and documentation of all changes to the data charting form and extracted datasets.

Only data from published studies will be included in this review. No individual participant data will be collected; therefore, ethical approval is not required.

Language restriction Only English language studies will be included in the review.

Country(ies) involved Canada.

Keywords muscle; skeletal muscle; protein; amino acids; leucine; resistance exercise; aging.

Contributions of each author

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