Amino Acids

https://doi.org/10.1007/s00726-026-03512-6

Article in Press

Adaptive crosstalk between polyamine metabolism, translation, and autophagy sustains energy homeostasis in mammals during starvation: a scoping review

Received: 12 December 2025

Accepted: 26 February 2026

Published online: 24 March 2026

Cite this article as: Karimi K., Roberts S.C., Carter N.S. *et al.* Adaptive crosstalk between polyamine metabolism, translation, and autophagy sustains energy homeostasis in mammals during starvation: a scoping review. *Amino Acids* (2026). https://doi.org/10.1007/s00726-026-03512-6

Kayhan Karimi, Sigrid C. Roberts, Nicola S. Carter, Sebastian J. Hofer & Reza Karimi

Adaptive crosstalk between polyamine metabolism, translation, and autophagy sustains energy homeostasis in mammals during starvation: A scoping review

Kayhan Karimi[1], Sigrid C. Roberts[1], Nicola S. Carter[1], Sebastian J. Hofer[2], Reza Karimi[1*]

[1] Kayhan Karimi, Pacific University School of Pharmacy, 222 SE 8th Avenue, HPC-Ste 451, Hillsboro, OR 97123, USA, Email: kari9098@pacificu.edu ORCID: https://orcid.org/0009-0008-2851-2100
[1] Sigrid C. Roberts, Pacific University School of Pharmacy, 222 SE 8th Avenue, HPC-Ste 451, Hillsboro, OR 97123, USA, Email: sroberts@pacificu.edu ORCID: https://orcid.org/0000-0002-0964-8554
[1] Nicola S. Carter, Pacific University School of Pharmacy, 222 SE 8th Avenue, HPC-Ste 451, Hillsboro, OR 97123, USA, Email: cartern@pacificu.edu ORCID: https://orcid.org/0000-0003-4720-1582
[2] Sebastian J. Hofer, Max Delbrück Center for Molecular Medicine (MDC), Robert-Rössle-Straße 10, 13125 Berlin, Germany, Email: Sebastian.Hofer@mdc-berlin.de ORCID: https://orcid.org/0000-0002-0756-0014
[1*]Corresponding author: Reza Karimi, Pacific University School of Pharmacy, 222 SE 8th Avenue, HPC-Ste 451, Hillsboro, OR 97123, USA, Email: karimir@pacificu.edu ORCID: https://orcid.org/0000-0003-3018-8326

Author contributions

Authors who had the idea for the article (Kayhan Karimi, Sigrid C. Roberts, Nicola S. Carter, Sebastian J. Hofer, Reza Karimi), who performed literature research and data analysis (Kayhan Karimi, Sigrid C. Roberts, Nicola S. Carter, Reza Karimi), who drafted the work (Kayhan Karimi, Reza Karimi) and critically revised the work (Kayhan Karimi, Sigrid C. Roberts, Nicola S. Carter, Sebastian J. Hofer, Reza Karimi).

Abstract

Mammalian cells tightly regulate the shift between catabolism and anabolism to maintain energy homeostasis during starvation. Among other adaptations, cells adapt to nutrient restriction by downregulating translation, the most energy consuming cellular process, and inducing autophagy. Polyamines are ubiquitous small polycationic endogenous metabolites indispensable for cellular growth and viability. They regulate both autophagy and translation processes, coordinating an intriguing metabolic hub during cellular adaptation to starvation. Recent studies have highlighted a complex role for polyamines during starvation and a growing body of evidence underscores various nutrients and nutrient-sensing pathways that modulate autophagy through their influence on the mammalian target of rapamycin complex 1 (mTORC1) signaling. mTORC1 is a master regulator of cellular anabolism, including translation. Less explored is how these coordinated systems adapt and respond to starvation. This scoping review explores how changes in polyamine metabolism and related molecules orchestrate the adaptive crosstalk between autophagy, mTORC1, and translation to ensure that the mammalian cell conserves energy to maintain essential cellular functions during starvation. Our review highlights that spermidine and its target, translation initiation factor 5A (eIF5A), facilitate translation of transcription factor EB (TFEB) to induce autophagy during starvation. Starvation suppresses mTORC1 activity, leading to reduced ribosome biogenesis and translation while promoting autophagy to meet cellular energy demands. We discuss the adaptive mechanisms by which reduced levels of acetyl-CoA, amino acids, EP300, glucose, insulin, and S-adenosylmethionine inhibit mTORC1 and simultaneously induce autophagy. Additionally, we describe the adaptive role that glucagon, Sestrin2, and urea play to inhibit mTORC1 and how eIF5A, glucagon, spermidine, and TFEB induce autophagy.

Key words: Amino acids, autophagy, mammals, mTORC1, spermidine, translation

Introduction

Polyamines are alkylamines that, being fully protonated at physiological pH, interact electrostatically with negatively charged DNA, RNA, proteins, and phospholipids (Mandal et al., 2013; Nakanishi & Cleveland, 2021; Sagar et al., 2021; Yu et al., 2015). As a result, polyamines play critical roles in replication, transcription, and translation and are important for cell signaling, functioning of the cytoskeleton, cell differentiation, cell proliferation, gene regulation, and apoptosis (Pegg, 2009; Sagar et al., 2021). Endogenous polyamines are synthesized in all organisms and their levels are tightly maintained and regulated by synthesis, degradation, dietary and cellular uptake, and release (Nakanishi & Cleveland, 2021; Ray et al., 2015; Sivashanmugam et al., 2017). Several tight regulatory mechanisms ensure that cellular polyamine levels are kept within a narrow range and altered polyamine levels have

been associated with neurological abnormalities, malignancies and age-associated diseases across various experimental models and clinical pathologies (Madeo et al., 2018; Moinard et al., 2005; Pegg, 2009; Zwighaft et al., 2015). Polyamines exhibit a plethora of metabolic functions, though the full range of their roles is still being discovered. In humans, polyamines are acquired through three sources: intestinal microorganisms, biosynthesis (endogenous), and dietary intake (exogenous) (Pinkerton & Barrientos, 2023; Sagar et al., 2021). One recent focus has been on the importance of polyamines during different phases of nutrient availability, including diet-induced obesity and fasting (Hofer, Daskalaki, Abdellatif, et al., 2024; Hofer, Daskalaki, Bergmann, et al., 2024; Mund et al., 2025; Ramos-Molina et al., 2019). In humans, cross-sectional studies report higher circulating spermidine (Spd) and spermine (Spm) in obese adults and children, including a study in obese children showing elevated Spm levels associated with metabolic and inflammatory markers (Codoñer-Franch et al., 2011). A clinical study on bariatric surgery showed altered circulating polyamine profiles, supporting the dynamic regulation of polyamines with weight change and possibly reflecting a fasting-like metabolic state after bariatric surgery (Ocaña-Wilhelmi et al., 2020). Fasting and diet-induced obesity, however, do not represent a simple metabolic mirror image of each other and their complex and distinct physiological impact remains to be fully elucidated.

Amino acids serve as essential molecules for translation as well as precursors for polyamines, neurotransmitters, hormones, purines, pyrimidines, and vitamins. Mammalian cells use 20 amino acids to synthesize proteins, including both essential and non-essential amino acids. Starvation increases muscle protein breakdown in order to release amino acids into the circulation with an ultimate goal to supply cells with energy (Torres et al., 2023). Thirteen amino acids are purely glucogenic, two are solely ketogenic, and five can be either glucogenic or ketogenic, in which their carbon skeleton is used to produce glucose (via gluconeogenesis) and ketone bodies (via ketogenesis), particularly during starvation (Emery, 2013; McGrath et al., 2023). The removal of the carbon skeleton from these amino acids produces a toxic byproduct, ammonia, which is converted to urea via the hepatic urea cycle, a pathway that is referred to as ureagenesis (McGuinness, 2026). Argininosuccinate synthetase 1 (ASS1) is a regulatory enzyme in the urea cycle that catalyzes metabolism of citrulline to argininosuccinate that, in turn, is metabolized to arginine (Arg) and fumarate by argininosuccinase (Hong et al., 2024; Hu et al., 2023). Arginase 1 (ARG1) catalyzes the conversion of Arg to urea and ornithine (Orn) through the urea cycle (Fox, 2022). ARG2 catalyzes the same reaction but is mainly found in mitochondria of cells from the kidney, small intestine, and brain (Fox, 2022; Grohmann et al., 2017). In essence, urea is the end product of protein catabolism and is excreted into urine. Other intermediate molecules produced as part of the ureagenesis pathway, such as fumarate and precursors for the polyamine pathway (Arg and Orn), are used in other metabolic pathways to support cell growth (Sivashanmugam et al., 2017). Anorexia nervosa has served as a representation of a human model of chronic starvation (Amorim et al., 2023). Numerous reports have indicated that blood urea nitrogen (BUN) is elevated in patients with anorexia nervosa (Caregaro et al., 2005; Lampert & Lau, 1976; Okabe, 1993; Stheneur et al., 2024; Tomita et al., 2014). While renal and pre-renal factors can cause serum BUN levels to increase, the elevated BUN is also explained by the fact that starvation leads to excessive protein degradation followed by ureagenesis and amino acid oxidation to generate glucose and ketone bodies through gluconeogenesis and ketogenesis pathways, respectively (McGuinness, 2026; Saxton & Sabatini, 2017).

Mammalian cells undergo a series of adaptive biochemical and physiological responses to cope with the stress of energy restriction, including the downregulation of protein synthesis which is the most energetically costly cellular process. While numerous studies have indicated molecular mechanisms and pathways that are important for cell survival during starvation (Bhowmick et al., 2024; Glick et al., 2010), less clear is how these pathways are coordinated and dynamically adjusted to preserve cell viability and energy balance under starvation conditions.

Cellular catabolism of energy-rich macromolecules (carbohydrates, lipids, and proteins) provides fuel in the form of ATP throughout multiple biochemical reactions that mostly are endergonic in nature (Karimi et al., 2021, 2024). These metabolic reactions are regulated by hormones including cortisol, insulin, glucagon and triiodothyronine to ensure adequate ATP supply in fed and fasted states (McGrath et al., 2023). Mammals have developed robust adaptive mechanisms to sustain energy homeostasis. The metabolic adaptations to a lack of calorie intake begin with the mobilization of stored glycogen from the liver and muscle (phase I), followed by the degradation of expendable proteins from muscle and oxidation of stored lipids from adipose tissue (phase II), and finally the degradation of essential proteins from all organs (phase III), marking a conceptual change from “fasting” to “starvation” (Lenaerts et al., 2006). Achieving a sustainable cellular homeostatic balance is complex and requires coordination of signaling networks to rapidly adjust the level of nutrients, such as glucose and amino acids, and other molecules, such as polyamines and hormones, to meet the specific demands of different organs in mammals.

Limited access to macronutrients during fasting is known to play a major role in inducing cellular macroautophagy (referred to hereafter as autophagy) in cells and model organisms (Mariño, Pietrocola, Madeo, et al., 2014). Evolutionarily, autophagy is a process that recycles cellular building blocks, as an adaptive response, to maintain energy homeostasis during starvation and cell damage (Bröer & Bröer, 2017; Laplante & Sabatini, 2012; Li

et al., 2023; Metur, 2024). Autophagy begins with the formation of a double membrane vesicle, engulfing cellular cargo to form an autophagosome that, upon maturation, fuses with lysosomes (Russell et al., 2014). In the resulting autolysosome, luminal acid hydrolases degrade cellular proteins, lipids, carbohydrates, nucleic acids, and organelles (Russell et al., 2014). In addition to autophagy's role to supply cells with nutrients, it is a critical cellular mechanism to eliminate superfluous materials such as damaged organelles and misfolded proteins that, when accumulated, may lead to toxic aggregates, liver tumor, neurodegenerative diseases, and various metabolic disorders (Ichimiya et al., 2020; Metur, 2024; Metur & Klionsky, 2024). Thus, autophagy plays an important role in maintaining the balance between degradation and nutrient/energy-supply, thereby supporting energy homeostasis (Metur, 2024; Metur & Klionsky, 2024; Russell et al., 2014). Autophagy is carried out by autophagy-related proteins (ATGs) (Chotechuang, 2010; Metur, 2024; Wesselborg & Stork, 2015). Over 40 genes are involved in autophagy, of which 18 have been identified to be essential for autophagosome formation in mammals (Metur, 2024; Noda et al., 2009). The synthesis of ATGs is regulated at transcriptional, post-transcriptional, translational, and post-translational levels (Lei & Klionsky, 2023; Metur, 2024).

Two well-known cellular signaling mechanisms serve as coordinators of cellular metabolism in the fed and fasted state to integrate metabolic information into autophagy regulation, the AMP-activated protein kinase (AMPK) and mammalian target of rapamycin (mTOR) (Y. Liu & Gu, 2022). While AMPK mainly senses glucose and the energy balance and becomes activated by a low ATP/ADP ratio to induce catabolism, mTOR is activated when the cells are enriched by nutrients and energy, as indicated by a high cellular ATP/ADP ratio (Y. Liu & Gu, 2022; Y.-P. Wang & Lei, 2018).

The regulatory serine/threonine kinase protein mTOR integrates signals from amino acids, oxygen, cell growth and proliferation, growth factors, and stress to maintain metabolic homeostasis (Dazert & Hall, 2011; Laplante & Sabatini, 2012; Russell et al., 2014). mTOR, evolutionarily conserved in all eukaryotes, is located in the cytoplasm of mammalian cells and is an essential part of the mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) (Lamming & Sabatini, 2013; Sabatini, 2017). Dysregulation of mTOR signaling is implicated in a variety of diseases including cancer (hematologic malignancies, skin, prostate, breast, and head and neck cancer), inflammation, neurodegeneration, and diabetes (Dazert & Hall, 2011; Huang, 2020). Both mTORC1 and mTORC2 are large subcomplexes with six and seven known protein components, respectively (Laplante & Sabatini, 2012). mTORC1 is a major repressor of autophagic flux (Saxton & Sabatini, 2017). A growing amount of evidence indicates that mTORC1's inactivation during nutrient deprivation plays an important role in the regulation of transcription, translation, and autophagy (Fîlfan et al., 2017; Grohmann et al., 2017; Sailer, 2012). In addition, mTORC1 is able to sense nitrogen availability and, as a result, responds to the availability of amino acids, particularly Arg, Leucine (Leu), and Methionine (Met) in mammals (Lauinger & Kaiser, 2021).

In this scoping review, our objective was to explore how the biosynthesis of polyamines, urea, and the translational apparatus were affected during starvation and how these are coordinated and integrated with other molecules and pathways to support energy homeostasis during starvation. Our review highlights several mechanisms of how a lack of nutrients triggers metabolic pathways and decreases mTORC1 activity, orchestrating the suppression of translation, and upregulation of autophagic flux. This review aims to summarize contributions of various molecules such as amino acids, acetyl-CoA, E1A binding protein p300 (EP300), insulin and glucagon hormones, Spd, eukaryotic initiation factor 5A (eIF5A), S-adenosylmethionine (SAM), and glucose that are directly or indirectly engaged to affect mTORC1 and autophagy during starvation.

Methods

In this scoping review, we have focused on the roles of cellular molecules and pathways that affect autophagy and translation during starvation. We have specifically kept our focus on the mammalian system to understand how energy homeostasis is maintained and how metabolic reprogramming is coordinated to protect mammals against the impact of starvation. The protocol for this review was formally registered on the online systematic review Open Science Framework (OSF) (DOI: 10.17605/OSF.IO/SZVW5).

The scoping review approach was undertaken based on the Joanna Briggs Institute (JBI) methodology in accordance with The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for scoping reviews (Aromataris & Riitano, 2014; Page et al., 2021; Peters et al., 2015). We conducted an electronic literature search for available evidence to address the study objective. While scoping reviews typically use Population, Concept, Context (PCC) framework, we adapted the Population, Intervention, Comparison, Outcome (PICO) structure to ensure that our search strategy captured specific intervention (polyamines, protein biosynthesis, and ureagenesis) during mammalian starvation. Four databases were included: Google Scholar, ScienceDirect, PubMed and Web of Science

(text availability: abstract and full text). Our search began on October 10th, 2024. The following subsections describe the search terms, strategies, selection process, data extraction, and synthesis.

Search Terms

We used a wide-range of terms in our literature search. The search terms used in our study were as follow: i) Google Scholar ("Mammals" AND "Starvation" AND "Polyamines" AND "(Protein biosynthesis OR Translation)" AND "Urea"); ii) ScienceDirect ("Mammals" AND "Starvation" AND "Polyamines" AND ("Protein biosynthesis OR Translation") AND "Urea"); iii) PubMed ("Mammals" AND "Polyamines" AND "Starvation", "Polyamines" AND "Starvation", "Anorexia Nervosa" AND "Polyamines", and "Anorexia Nervosa" AND "Urea"; and iv) Web of Science ("Mammals" AND "Polyamines" AND "Starvation", "Polyamines" AND "Starvation", "Anorexia Nervosa" AND "Polyamines", and "Anorexia Nervosa" AND "Urea"). We did not limit our search to any specific date. As a result, the time frame of publication for the abstracts and articles was between 1972 to March 2025.

Search Strategy

We conducted a literature search and focused on published peer-reviewed studies, as well as gray literature. In order to ensure that we accurately selected pertinent data, at least two authors screened each title and abstract to assess their suitability and ensure that the abstract matched the inclusion criteria. When an article provided supporting background information for our research objective, even if it was not directly related to starvation, such as with cancers, we retrieved the full-text article to ensure that we did not miss any relevant information.

Inclusion Criteria

In our search engine, we used our search terms and included all relevant articles, full texts, and abstracts. In addition, we screened the reference list of articles to identify potentially relevant information. If a full article was not accessible but the abstract indicated that the data would be relevant in our review study, we used our library system to order the article.

Exclusion Criteria

We excluded articles containing medication use, because medications can change how an organism reacts to starvation. In addition, we excluded studies not written in English or where the full text was missing, or that did not include mammals, or were related to binge eating/purging disorders (bulimia).

Selection Process

Four authors (screeners) of this review study participated in the review of published abstracts to ensure that each published article matched inclusion criteria and the article was relevant to our review study. In any case in which there was an uncertainty whether an abstract would produce any useful information, screeners decided to include the abstract into our extraction spreadsheet for a further review and analysis of its full-text.

Data Extraction and Synthesis

All extractions were carried out by screeners. With keeping the PRISMA flow diagram in mind, we followed a structured process to extract any necessary data into an Excel spreadsheet. Data extraction from each study included multiple study characteristics/domains that included information for authors, title of the study, journal name, year, aims/purpose, population and sample size, source of evidence, methodology, and outcomes of the published articles. We used a color code approach to indicate that at least two independent authors agreed that the identified results from abstracts matched the inclusion criteria. When necessary, authors provided comments in the Excel spreadsheet to inform each other about why an abstract was relevant or irrelevant. After the search and extraction of data were complete, duplications and irrelevant extracted data were removed from the Excel spreadsheet.

Our preliminary search terms did not include "mTORC1" or "autophagy", however, they surfaced as recurring key themes linked to starvation and translation during the full-text review of eligible articles. As a result, we included their adaptive roles in our study. For the synthesis of data, we focused on the following pathways or mechanisms that were affected during starvation when reviewing a full-text article for any relevant data: ureagenesis, amino acids, polyamines, hormones (insulin and glucagon), translation, eIF5A, autophagy, and apoptosis. When all full-text articles were retrieved, the first and corresponding authors evaluated the suitability of all relevant full-text articles. Findings from relevant primary research papers, theses, book chapters, and review articles were summarized to generate a rough draft of synthesis. A fifth author joined our team to review the above data and participate in the synthesis of the manuscript. Thereafter, all five authors reviewed and edited the draft to ensure that the study's objective and the outcome of the study was clear, unbiased, and accurate.

Results

Characteristics of included work

A total of 797 records were identified from four databases and upon reviewing the abstracts, a total of 641 of the abstracts did not match the inclusion criteria. Our search process resulted in identifying 113 full-text articles. After excluding additional 40 full-text articles, due to not being related to the objective as described in the following PRISMA flow diagram, a total of 73 full-text studies remained and were included for this review (Fig. 1).

We mapped full-text articles to a series of characteristics as described in the methods. The nature of the eligible studies was five book chapters, twelve theses, thirty review studies, thirteen animal studies, six clinical studies, and seven *in vitro* cell culture studies. Table 1 summarizes the characteristics of the identified full-text scientific literature resources containing data that assisted us in meeting our objective. As shown in Table 1, our data indicate that starvation impacts a variety of cellular molecules as well as biochemical and nutrient-sensing pathways. More detailed data are presented in the following results and discussions sections.

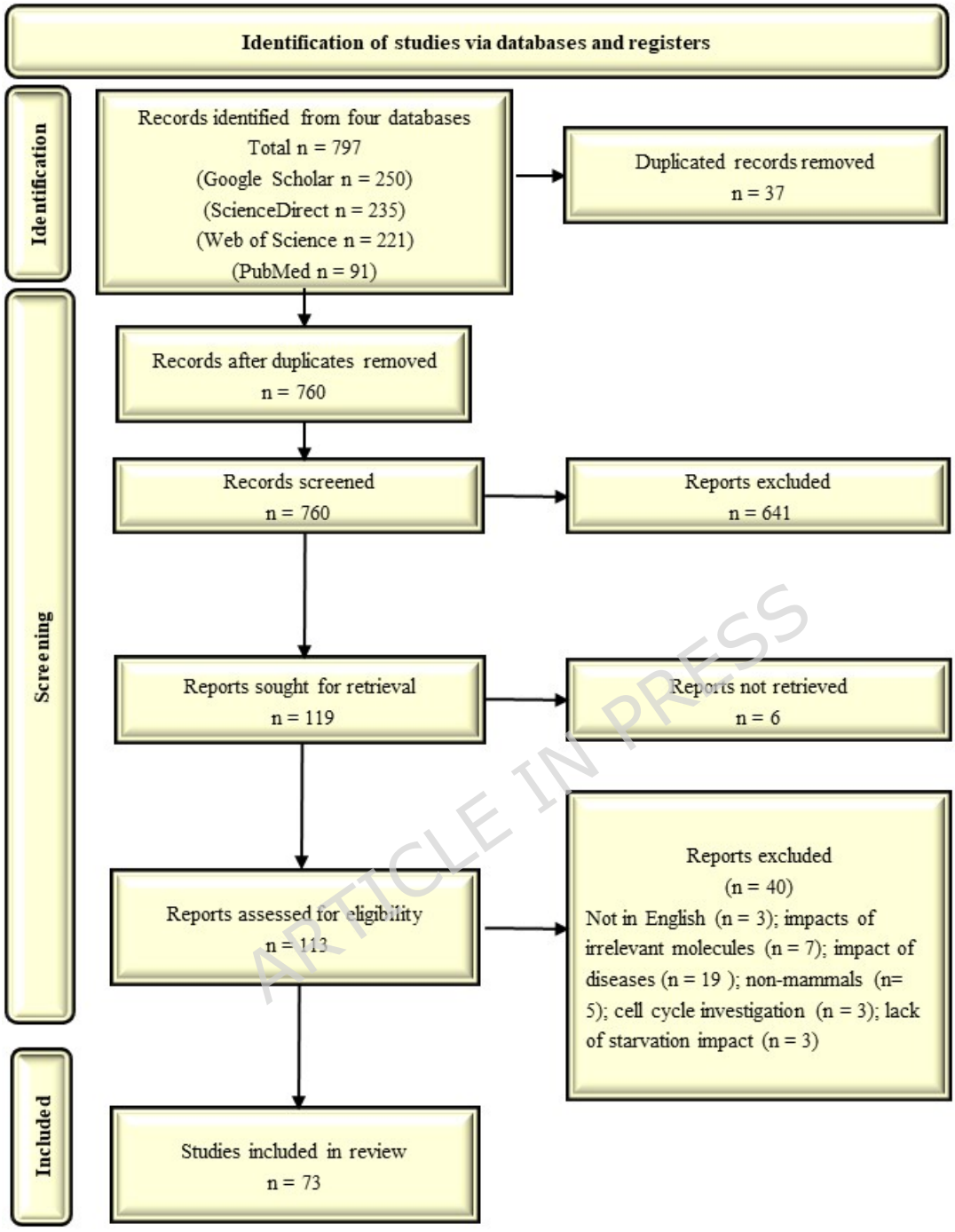

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram used to indicate the number of reports that were searched and identified from the four databases for the scoping review process (Page et al., 2021). A total 797 articles were identified in the initial search and upon stepwise review, a total of 73 eligible articles were included in this study

Metabolic roles of polyamines in ureagenesis during starvation

Polyamines are polycationic organic molecules with two or more amino groups (Fig. 2). The amino acid Arg plays an important role in the synthesis of polyamines. ARG1 is mainly found in the cytoplasm of hepatic cells and catalyzes conversion of Arg to Orn through the urea cycle (Fig. 2) (Fox, 2022; G. Wu & Morris, 1998). Experiments with primary cultures of rat aortic smooth muscle cells indicated that polyamine biosynthesis was reduced or increased when the expression of ARG1 was inhibited or stimulated, respectively (Fox, 2022; Morris, 2007; L. H. Wei et al., 2001). Accordingly, ARG1 serves as a regulatory factor in polyamine biosynthesis (Morris, 2007).

High levels of Arg promotes mTORC1-facilitated cell growth and Arg starvation prevents mTORC1 from sensing the availability of amino acids (Albaugh et al., 2017; Alexandrou et al., 2018; Blagih, 2015). In addition, Arg starvation causes autophagy and apoptosis (Albaugh et al., 2017; Changou et al., 2014). There is a considerable body of evidence to suggest that autophagy and apoptosis are interconnected, i.e., if autophagy is not initiated to support cell survival in damaged cells, apoptosis is activated to induce an efficient clearance of cell debris (Fîlfan et al., 2017; Kroemer et al., 2010).

Ornithine decarboxylase (ODC) is the initial enzyme in the polyamine biosynthetic pathway. ODC is a rate-limiting enzyme that catalyzes the conversion of Orn to the diamine putrescine (Put), in a pyridoxal phosphate (PLP)-dependent reaction. Put is further catalyzed to Spd, a triamine, and Spm, a tetraamine, by spermidine synthase (SRM) and spermine synthase (SMS), respectively (Fig. 2) (Carter et al., 2022; Nakanishi & Cleveland, 2021; Proietti et al., 2020; Zahedi et al., 2022). It is widely accepted that the biosynthesis of polyamines is determined mainly by ODC activity (Schertel & Eichler, 1991).

The levels of cellular polyamines are tightly regulated as they play essential roles in a variety of cellular functions, including stabilization of DNA, regulation of gene expression, RNA processing, functioning of cytoskeletons, translation and post-translation modification, pathogenesis of cancer, and neural growth and development (Childs et al., 2003; Grohmann et al., 2017; Munro et al., 1975; Sagar et al., 2021; Zahedi et al., 2022). In the urea cycle, Orn interacts with carbamoyl phosphate to produce citrulline, a reaction catalyzed by ornithine transcarbamylase. Furthermore, Orn serves as a substrate for ornithine δ-aminotransferase (OAT) to produce the amino acid proline (Pro) (Grohmann & Bronte, 2010). Orn is thereby an essential intermediate molecule in the synthesis of Arg, polyamines, and Pro, as well as for the disposal of the ammonia produced from amino acid catabolism, via the urea cycle (Fig. 2) (Grohmann et al., 2017; Narayan, Kapil Singh and Kashyap, Reenu, 2021).

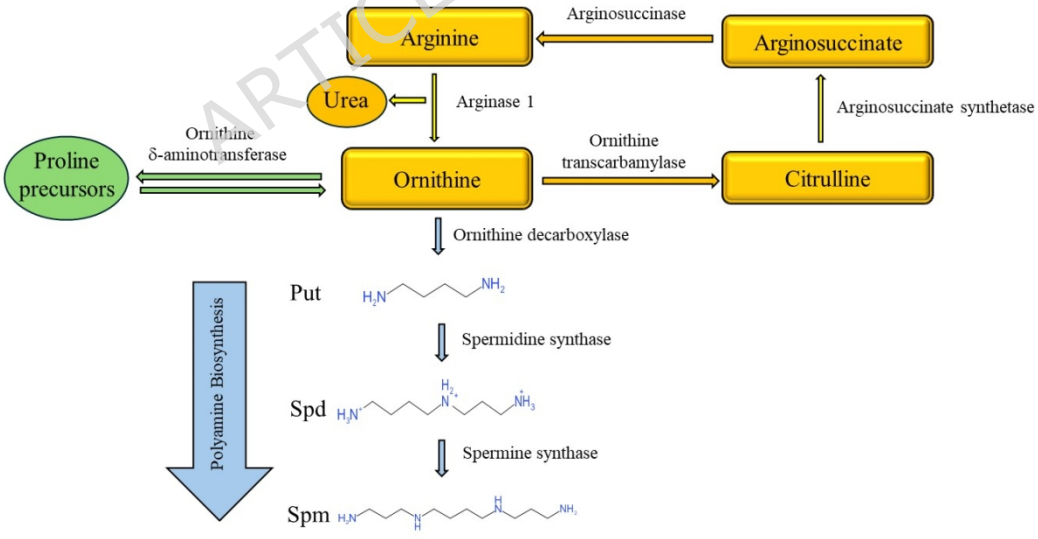

Fig. 2 The multifactorial roles of ornithine in mammals: Ornithine (Orn), in the cyclic pathway of ureagenesis, is synthesized from arginine and plays a central role in the biosynthesis of proline, urea, and polyamines. The rate-limiting enzyme, ornithine decarboxylase, uses Orn to catalyze biosynthesis of putrescine (Put). Subsequent metabolism of Put produces spermidine (Spd) which is converted to spermine (Spm) with spermidine synthase and spermine synthase, respectively. These three small molecules (Put, Spd, and Spm) are the only polyamines that are

synthesized in mammals. The reversible pathway (green) that produces Orn from proline precursors includes two intermediate products that are not shown here. Reactions that are part of the urea cycle are highlighted in orange

During starvation, the increased catabolism of proteins and the oxidation of amino acids leads to an increased urea cycle activity (Urschel, 2007; Viola & Bronte, 2007). Since the activation of mTORC1 to control translation depends on the availability of amino acids (particularly Leu and Arg) (Takahara et al., 2020), it is likely that the degradation of amino acids and, consequently, the production of urea, will negatively impact mTORC1's effect on protein synthesis. Emerging evidence suggests that urea is no longer merely a wasteful or inert byproduct of protein metabolism (Ivanovski et al., 2005; H. Wang et al., 2019). For instance, in mice it was shown that urea (or its byproduct, cyanate) carbamylates mTOR and inhibits mTORC1- ribosomal protein 6 kinase (S6K) dependent protein synthesis in dendritic cells which highlights a regulatory role that urea plays in mTORC1 signaling (H. Wang et al., 2019). Further research, however, is required to fully clarify the role of urea in its effects on mammalian cells.

As mentioned earlier, Orn plays multifactorial roles in mammalian cells. During limited protein turnover or low Arg levels, OAT works in a reverse reaction to produce Orn from proline precursors (glutamate γ-semialdehyde and Δ1-pyrroline-5-carboxylate) (Nelson et al., 2021) (Fig 2). The synthesized Orn is then used in the urea cycle to produce citrulline and Arg. OAT is found in the mitochondrial matrix of most tissues, particularly in the liver, intestine, brain and kidney (Ginguay et al., 2017). Expression levels of OAT are downregulated in the mouse small intestine after 24 hours of fasting (Lenaerts et al., 2006). Much of our understanding regarding adaptive neuroendocrine responses during prolonged starvation stems from studying patients with anorexia nervosa (Amorim et al., 2023). In a retrospective study that investigated laboratory parameters from clinical records of adolescents with anorexia nervosa, serum urea was found to be 25% higher compared with the reference value (Pires et al., 2020). While the neuroendocrine impact on ureagenesis is yet to be established, elevated urea levels underscore the adaptive role of amino acid oxidation during starvation. In addition, since the pathophysiology and neurobiological implications of anorexia nervosa may affect laboratory data, the observed elevated ureagenesis should be interpreted within the complexity and confounding effects of anorexia nervosa. In a rat model, animals in the fast state had 60% less ornithine transcarbamylase activity in comparison to the fed state (Weber et al., 1972). These data suggest that when urea production is elevated during starvation, excessive Orn is pulled into metabolic demands such as Pro production and polyamines biosynthesis through interactions or competitions between OAT and ODC (Fig. 2). The impact of starvation to downregulate OAT and to suppress ornithine transcarbamylase suggests an adaptive mechanism whereby Orn may be channeled into polyamine biosynthesis.

Metabolic roles of polyamines in autophagy during starvation

Autophagy dysfunction is involved in different human diseases (Alzheimer's, Huntington's, diabetes, and different kind of tumors and neurodegenerative diseases) and affecting effector properties of central cellular components of innate and adaptive immunity to fight bacteria, viruses, and parasites (Fîlfan et al., 2017; Klionsky et al., 2021; Levine et al., 2011; Rubinsztein et al., 2012). For instance, there is data that indicates that autophagy stimulation might be useful against vascular disease by stimulating cholesterol efflux to inhibit necrotic core formation and lipid accumulation (Fîlfan et al., 2017; Michiels et al., 2016). Upregulation of autophagy is recognized as one of the key cellular responses to nutrient deprivation (Russell et al., 2014). As an example, mice starved for 24–48 hours display increased numbers of autophagosomes in most tissues and starvation for 24 hours leads to the down-regulation of proteins involved in protein synthesis and amino acid metabolism (Lenaerts et al., 2006; Mizushima, 2010). Autophagy is a critical cellular mechanism to maintain adequate levels of amino acids for both protein synthesis and gluconeogenesis (Neves et al., 2015). The effects of aging on the regulation of rat liver autophagy have shed more light on the impact of fasting on autophagy in mammals. Rats' livers show activated autophagic flux after overnight fasting. However, this induced autophagy was delayed already after 6 months of age and almost undetectable at older age, which was ameliorated by caloric restriction (Del Roso, 2003). It has been reported that autophagy particularly responds to the cellular levels of Arg, Met, and the branched chain amino acids (BCAAs) (Albaugh et al., 2017; Lauinger & Kaiser, 2021; Russell et al., 2014; R. Wu, 2020).

Cellular levels of polyamines are tightly regulated by coordinated biosynthesis, degradation, uptake, and efflux (Holbert et al., 2020; C. Zhang et al., 2025). Dysregulated polyamine profiles are implicated in aging, cognitive impairment, and various cancers (particularly skin and colon cancer) while an optimal quantity of polyamines is suggested to delay cardiovascular diseases and to increase longevity (Sagar et al., 2021). The polyamine Spd is known to decrease with aging in humans (Alsaleh et al., 2020; Eisenberg et al., 2009; Fîlfan et al., 2017). While the mechanisms governing biological aging are complex, growing evidence implies that Spd plays a regulatory role in aging *via* autophagy by promoting longevity in multiple organisms (Eisenberg et al., 2009, 2016; Ghosh et al., 2020; J.-K. Liu, 2022; Madeo et al., 2019; Minois et al., 2012; Pinkerton & Barrientos, 2023; H. Zhang et al., 2019). In

addition, Spd plays a key role in maintaining immune resilience, particularly, by enhancing CD8+ T cell responses to infection and vaccines in aged mice in an autophagy-dependent manner (Kelly & Pearce, 2020; Puleston et al., 2014).

In addition to Arg, Met is also required for polyamine biosynthesis, as a source of an aminopropyl moiety (Fig. 3) (Parkhitko et al., 2020; Sagar et al., 2021; R. Wu, 2020). Met serves as a substrate for glutathione formation, initiation and elongation of translation, and in the formation of SAM. SAM is important for polyamine biosynthesis and as a methyl donor in numerous metabolic reactions (Chisari et al., 2021; Montalbano et al., 2023; Vernieri et al., 2016). Met interacts with ATP to generate SAM, a reaction catalyzed by methionine adenosyltransferase (MAT) (Ouyang et al., 2020). It is well documented that SAM is the sole methyl group donor involved in the methylation of DNA, RNA, and histones. In addition, SAM is essential for the biosynthesis of the polyamines Spd and Spm and for the regulation of autophagy in mammals (Ouyang et al., 2020). In 2017, Gu et al identified a new critical protein called S-adenosylmethionine sensor upstream of mTORC1 (SAMTOR) (Gu et al., 2017). When mammalian cells are starved for Met, SAM levels are reduced causing SAMTOR to associate with another protein, GTPase activating protein toward Rags-1 (GATOR1). The SAMTOR-GATOR1 complex ultimately results in the inhibition of mTORC1, hence inducing autophagy (Gu et al., 2017; Kitada et al., 2020; Lauinger & Kaiser, 2021). These data emphasize the important role that Met plays in the activation of autophagy (Fig. 3).

In addition to the critical role that Met plays in autophagy, cellular Met's availability is crucial for the synthesis of Spd and Spm. The enzyme S-adenosylmethionine decarboxylase (SAMDC) catalyzes the conversion of SAM to decarboxylated S–adenosylmethionine (dcSAM) which provides the aminopropyl group in the Spd and Spm molecules (Fig. 3) (Ray et al., 2014). SAMDC has a short half-life (20-60 minutes) that implies it performs specific cellular tasks that require rapid activity and turnover (Ast, 1995). Further research, however, is necessary to elucidate the precise cellular role that SAMDC plays during starvation. Outside of its role in polyamine catabolism, SAM is converted to S-adenosylhomocysteine (SAH), and upon donation of its methyl group, it can then be hydrolyzed into adenosine and homocysteine by SAH hydrolase enzyme (Fig. 3) (Lauinger & Kaiser, 2021).

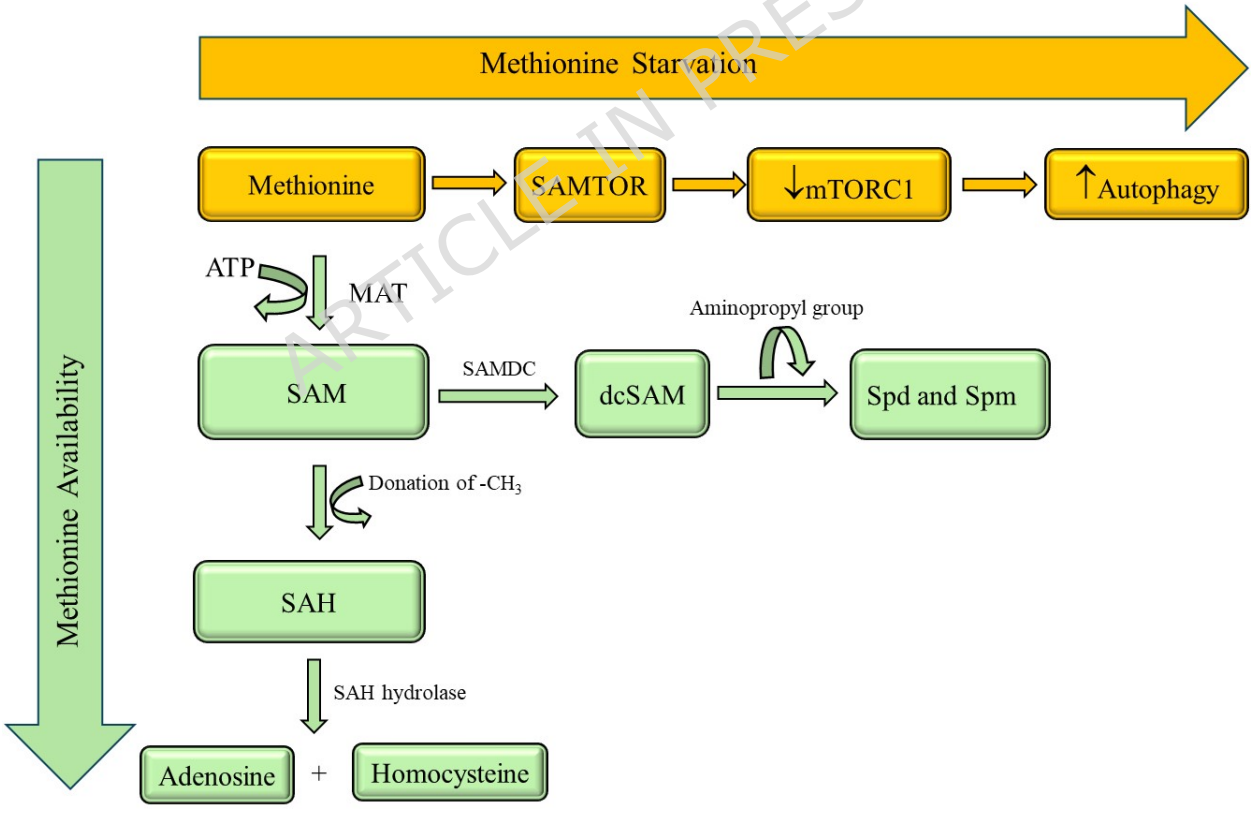

Fig. 3 The versatile roles of methionine in the polyamine biosynthesis, mTORC1 signaling, induction of autophagy, and production of homocysteine. In the fed state (green color) methionine is converted to S-adenosylmethionine (SAM) by the methionine adenosyltransferase enzyme (MAT). S-adenosylmethionine decarboxylase (SAMDC) catalyzes the removal of the carboxyl group from SAM to form decarboxylated S–adenosylmethionine (dcSAM) which serves as the donor of the aminopropyl group required for the synthesis of spermidine (Spd) and spermine

(Spm). SAM also undergoes further metabolism to S-adenosylhomocysteine (SAH) which is then hydrolyzed into adenosine and homocysteine by SAH hydrolase enzyme. On the other hand, when there is limited methionine (orange color), SAMTOR is activated to inhibit mTORC1 and induce autophagy. The upward arrow indicates "increase" and the downward arrow indicates "reduction" in the molecular levels or metabolic outcomes during starvation. SAMTOR, S-adenosylmethionine sensor upstream of mTORC1

Less is known about the direct changes of polyamine metabolism during fasting. Recently, it was shown that fasting increases Spd levels in yeast, flies, mice, human plasma, and peripheral blood mononuclear cells (PBMCs), while Orn and Put largely decreased in many murine tissues (Hofer, Daskalaki, Bergmann, et al., 2024). Given its role in autophagy regulation, indeed, Spd biosynthesis was key to fully elicit elevated autophagy upon fasting (Hofer, Daskalaki, Bergmann, et al., 2024).

Polyamines are known to increase the efficiency and fine-tune the translation of a specific set of genes referred to as "polyamine modulon" in both prokaryotic and eukaryotic organisms, including mammals (Igarashi & Kashiwagi, 2011). Relevant examples here are genes that code for eIF5A and antizyme proteins in humans (Proietti et al., 2020). A role for eIF5A in autophagy regulation was demonstrated by the observation that autophagy induction or starvation increased the association of eIF5A with ribosomes in Michigan Cancer Foundation-7 cells (MCF-7 cells are human breast cancer cell line), which in turn promotes autophagosome formation (Lubas et al., 2018). This offers one explanation how polyamines impact the autophagic machinery.

The translation initiation factor, eIF5A, plays an essential role in regulating and enhancing the process of autophagy and relies on Spd for its unique post-translational modification and activation. Briefly, Spd donates its aminobutyl moiety to Lys50 of the eIF5A to form the hypusine residue, a reaction catalyzed successively by deoxyhypusine synthase (DHPS) and deoxyhypusine hydroxylase (DOHH) (Cano et al., 2008; Park & Wolff, 2018; Sagar et al., 2021). It has been shown that eIF5A is one of the most expressed proteins in activated T cells and dysregulation of the hypusination process is associated with various pathological conditions, including cancer and diabetes (Hukelmann et al., 2016; Puleston et al., 2017; Wątor et al., 2023). To this date, no other mammalian proteins have been identified to undergo this unique post-translational modification. Recent studies have indicated that this sole hypusination process is key during fasting in many organisms (Hofer, Daskalaki, Bergmann, et al., 2024).

The role of hypusinated eIF5A is to support translation of proteins that have polyproline residues (Tseng, 2023). Cryo-EM has shown that the hypusine moiety contacts A76 of the CCA-end of the P-site tRNA to stabilize the region which ultimately rescues the stalled ribosome and promotes peptide bond formation for Pro-Pro residues (Melnikov et al., 2016; Pavlov et al., 2009; Schmidt et al., 2016; Schuller et al., 2017; Wątor et al., 2023, 2023). Among other proteins, hypusinated eIF5A is important for the translation of transcription factor EB (TFEB) in B cells of both mice and humans (Fig. 4A) (H. Zhang et al., 2019). TFEB is a mammalian autophagosomal and lysosomal master regulator of autophagy and therefore links polyamines to global autophagy regulation via TFEB translation. Consequently, mouse and human TFEB variants contain one and two triproline motifs, respectively, which explains how hypusinated eIF5A controls TFEB translation (H. Zhang et al., 2019).

Metabolic roles of spermidine and acetyl-CoA in EP300-mediated autophagy during starvation

Another mechanism by which Spd may control autophagy is via histone acetyltransferase activity. Spd competitively inhibits the acetyltransferase enzyme, EP300, which results in an overall reduction of acetylation levels of histones. Altered histone acetylation leads to a significant upregulation of multiple ATGs in different organisms, including human cells (Eisenberg et al., 2009; Li et al., 2023; Neves et al., 2015; Pietrocola et al., 2015). Since fasting causes inhibition of EP300 and stimulation of autophagy (Hofer et al., 2022; Kaushik et al., 2021) the above Spd mechanism suggests that during starvation, elevated Spd levels might be required to coordinate EP300 inhibition in order to promote autophagic flux (Fig. 4 A and B).

The influence of acetyl-CoA on autophagy is also mediated by EP300 (Fig. 4B). Acetyl-CoA plays a crossroad role during the metabolism of macronutrients. Acetyl-CoA is produced, upon metabolism of carbohydrates, proteins, and lipids, in mammals to enter the citric acid cycle to produce energy-rich molecules (GTP, NADH, $FADH_2$). Reduced levels of cellular acetyl-CoA trigger autophagy in mammals (Mariño, Pietrocola, Madeo, et al., 2014; Schroeder et al., 2014; Zhou et al., 2019). This occurs because acetyl-CoA is the essential substrate for the acetyltransferase enzyme EP300, which transfers acetyl groups to key autophagy proteins (ATG5, ATG7, ATG12, and LC3). By acetylating these proteins, EP300 inhibits their pro-autophagic activity, so when acetyl-CoA levels drop, this inhibition is lifted, allowing autophagy to proceed (Mariño, Pietrocola, Madeo, et al., 2014). Reduced levels of acetyl-CoA might also have other consequences which can trigger autophagy, for instance, changes in other histone acetylases and a reduced ATP/AMP ratio promoting AMPK activity. It is worth noting that reduced levels of acetyl-CoA or a direct inhibition of EP300 by other methods results in a rapid activation of AMPK and inactivation of

mTORC1, which suggests that these two nutrient-sensing pathways are functionally connected to each other (Mariño, Pietrocola, Eisenberg, et al., 2014).

mTORC1 also stimulates adipogenesis and lipogenesis in white adipose tissue (WAT) (Torres et al., 2023). Since acetyl-CoA is an important precursor for the biosynthesis of fatty acids, its role during starvation might extend to the regulation of lipid metabolism. Further studies, however, are needed to indicate whether there is a signaling pathway between acetyl-CoA and mTORC1 in adipogenesis and lipogenesis during starvation.

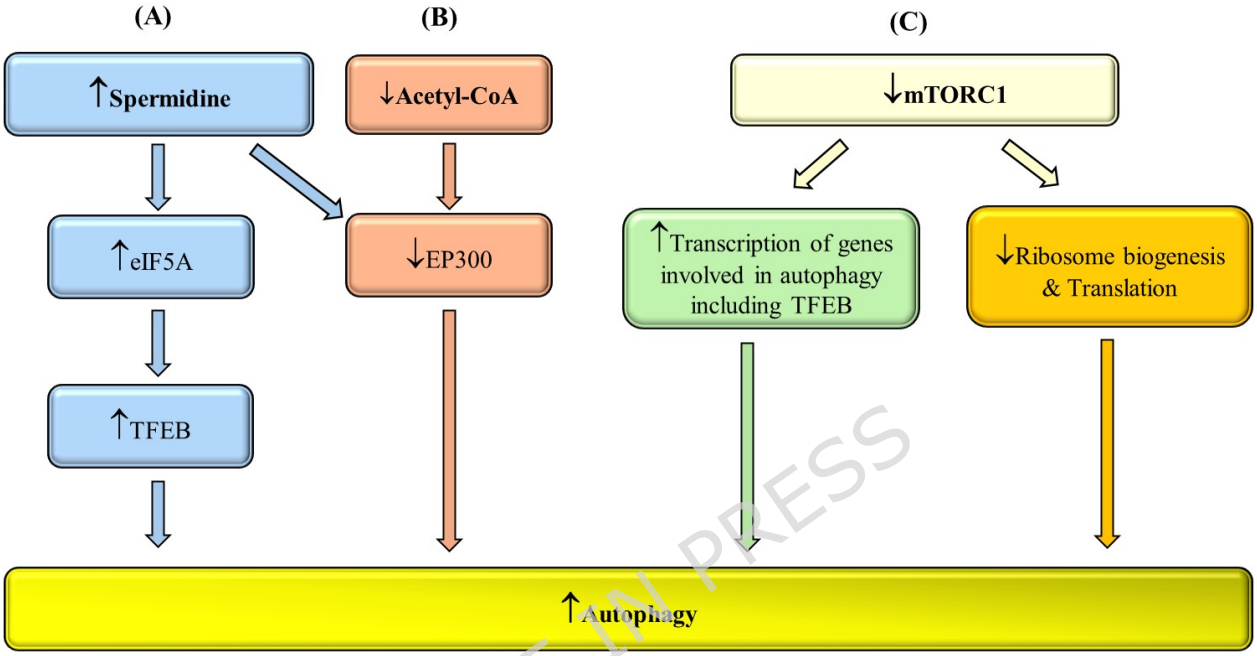

Fig. 4 Induction of autophagy by different mechanisms and molecules during starvation. **A.** Spermidine's effect on eIF5A stimulates the translation of TFEB, which subsequently induces autophagy. In addition, spermidine-mediated suppression of EP300 during starvation ultimately results in the induction of autophagy. **B.** Acetyl-CoA-mediated suppression of EP300 resulting in the induction of autophagy. **C.** The impact of mTORC1 inhibition on transcription of autophagic genes, ribosome biogenesis, and translation, that results in autophagy. Upward arrow indicates "increase" and downward arrow indicates "reduction" in the molecular levels or metabolic outcomes during starvation. eIF5A, Eukaryotic initiation factor 5A; EP300: E1A-associated protein p300; TFEB, Transcription factor EB

Metabolic role of mTORC1 signaling in translation and transcription during starvation

mTORC1 targets and controls the translational apparatus, prominently the translation initiation factor 4E-binding protein 1 (4E-BP1) and S6K (Bröer & Bröer, 2017; Christian, 2002; Hong et al., 2024; Pinkerton & Barrientos, 2023; Russell et al., 2014; Z. Wei et al., 2021). Briefly, mTORC1 phosphorylates 4E-BP1 at multiple sites, which causes dissociation of 4E-BP1 from the eukaryotic initiation factor eIF4E, leading to 5′cap-dependent mRNA translation (Chotechuang, 2010; Saxton & Sabatini, 2017). mTORC1 directly phosphorylates S6K which plays a critical role in facilitating mRNA transcription, splicing, and protein synthesis (Morris, 2016; X. Wu et al., 2022).

The inhibition of mammalian translation is also an adaptive response to amino acid starvation to conserve energy resources. A consequence of amino acid starvation is the suppression of eukaryotic initiation factor 2B (eIF-2B) in rabbit reticulocyte lysate. The function of eIF-2B is to catalyze the exchange of GTP for GDP bound to eIF2 during the initiation of translation (to convert inactive eIF2-GDP to active eIF2-GTP). As a result, the suppressed eIF-2B inhibits the activation of eIF2-GTP, which ultimately blocks translational initiation (Gross & Rubino, 1989).

Ribosome biogenesis is essential for maintaining a functioning translational apparatus; however, it is also metabolically expensive (Szaflarski et al., 2022). mTORC1 also directly controls translation rates by regulating ribosome biogenesis (Fig. 4C). In addition, mTOR signaling is inhibited during starvation to promote transcription of genes that are involved in autophagy (Fig. 4C) (Russell et al., 2014). mTORC1 facilitates the transcription of 5S rRNA

and transfer RNA (tRNA), which promotes translation (Kantidakis et al., 2010; Laplante & Sabatini, 2012). mTORC1 activity also affects translation rates by controlling transcriptional factors. For instance, it regulates RNA polymerase I (Pol I) activity by promoting ribosomal RNA transcription through a process involving protein phosphatase 2A (PP2A) and transcription initiation factor IA (TIF-IA). TIF-IA is also a regulatory factor that responds to nutrient and growth-factor availability (Laplante & Sabatini, 2012; Mayer et al., 2004).

Transcription of 45S pre-rRNA results in eukaryotic 18S, 5.8S and 28S rRNAs production. These rRNAs then combine with ribosomal proteins to form the 40S and 60S ribosomal subunits, which ultimately assemble into the 80S ribosome (Fyfe et al., 2018). Synthesis of the 45S pre-rRNA in rats' liver is inhibited after 24-hour starvation which ultimately suppresses translation (Munro et al., 1975). Since mTORC1 promotes RNA polymerase I, which in turn promotes synthesis of 45S pre-RNA, mTORC1 stimulates ribosome biogenesis to support translation during the fed state. The data described above suggest that the inhibition of mTORC1 is an adaptive response during starvation to reduce the cellular energy expenditure caused by the translational apparatus.

Apart from the regulation of general translation, mTORC1 also controls regulation of TFEB that is necessary for maintaining adequate lysosome biogenesis during high autophagic flux (Russell et al., 2014) (Fig 4C). Thereby, TFEB is one of the nexuses where polyamine-specific and mTORC1-specific control of autophagy converge. In the fed state, mTORC1 phosphorylates and thereby inhibits TFEB, limiting its nuclear translocation and the expression of TFEB-dependent genes that are necessary for lysosomal biogenesis. In the starvation state, mTORC1 is inhibited and TEFB is dephosphorylated/activated, which was shown in murine primary hepatocytes (Settembre et al., 2012). It is, however, unclear whether the nuclear translocation of TFEB during starvation occurs in all eukaryotic cell types equally.

Antizyme is implicated in the regulation of autophagy and polyamine metabolism during starvation

The intracellular polyamines levels are regulated at several steps which includes their dietary uptake, cellular biosynthesis, microbial biosynthesis, organismal distribution, as well as degradation and excretion. ODC activity determines, to a large extent, the levels of tissue polyamines and degradation of ODC is accelerated by high levels of polyamines (Pegg, 2009; Ray et al., 2015). A major cellular inhibitor of polyamine biosynthesis is the ODC-inhibiting protein antizyme (AZ), a regulatory protein whose synthesis is increased upon high levels of cellular polyamines (Pegg, 2009). AZ noncovalently forms AZ-ODC complexes to inhibit ODC activity and promote its degradation (Ivanov & Atkins, 2007; Ramos-Molina et al., 2014). High cellular levels of Spd directly induce the synthesis of AZ to inhibit ODC *via* a negative feedback mechanism, thereby balancing cellular polyamine biosynthesis in response to the metabolites' availability (Ray et al., 2014; Stegehake et al., 2015). This polyamine-conferred regulatory process involves a unique +1 ribosomal frameshifting mechanism that is triggered by increasing polyamine levels, allowing the AZ's correct translation (Ivanov & Atkins, 2007; Ray et al., 2014, 2015). It has been demonstrated that this polyamine-driven induction may be dependent on mTORC2, as inhibition of mTORC2 suppresses production of AZ even when polyamine levels are high (Ray et al., 2015). Amino acid starvation leads to the inhibition of mTORC1 and activation of mTORC2 which ultimately results in the induction of AZ synthesis (Ray et al., 2012). Taken together, these data suggest that starvation activates multiple, parallel pathways, inhibiting mTORC1 to increase autophagy and requiring mTORC2 activity to allow AZ facilitated inhibition of polyamine synthesis. mTORC2 signaling is less understood and is beyond the scope of our study. While a direct link between mTORC1 and AZ synthesis has not been established yet, it is known that activation of mTORC1 induces polyamine synthesis (Gomes et al., 2017). The inhibition of mTORC1 and global translation during starvation has been linked to changes in polyamine anabolism, thereby increasing autophagy while also limiting polyamine-controlled translation.

Metabolic role of glucose in mTORC1 signaling during starvation

The fundamental roles that glucose, insulin and glucagon play in regulating energy homeostasis during periods of food deprivation has been extensively studied and is beyond the scope of this review. However, we found intriguing data relevant to our study that warrants a brief mention here. Our review indicated an interplay among glucose, BCAAs, insulin, and mTORC1 signaling during starvation.

The link between glucose and mTORC1 is supported by the role of glyceraldehyde 3-phosphate dehydrogenase (GAPDH) in glycolysis. GAPDH directly and negatively regulates mTORC1 signaling (Lee et al., 2009). During starvation (when glucose is less available), GAPDH binds the small GTPase protein Rheb, preventing it from binding mTOR and thereby inhibiting mTORC1 signaling (Lee et al., 2009). This inhibitory mechanism suggests that during low-glucose conditions, the suppression of glycolytic flux serves to inhibit mTORC1 through an adaptive mechanism which ultimately results in conserving cellular energy expenditure. In the above study, the authors also used Tuberous sclerosis 1 (TSC1)-deficient cells and AMPK-silenced cells which indicated that the GAPDH-Rheb pathway occurred independently of the AMPK axis.

Insulin, a hormone released in response to high carbohydrate levels, acts as a key signal that activates the mTORC1 pathway and suppresses autophagy (Naito et al., 2013; Neves et al., 2015). In response to starvation, insulin decreases and glucagon increases which ultimately leads to an induction of autophagy (Bergamini et al., 2007; Kiffin, 2010). Additionally, it is suggested that autophagy is differentially regulated by insulin in a tissue-dependent manner in the liver and skeletal muscle of mice (Naito et al., 2013).

During starvation, hormonal levels of glucagon increase cellular BCAAs uptake and stimulate their oxidation to produce ATP (Bifari & Nisoli, 2017; Neinast et al., 2019). BCAAs include the essential amino acids Leu, valine (Val), and isoleucine (Ile) that mammals obtain from animal or plant-based foods. They are hydrophobic, metabolized in extrahepatic tissues (mostly in the adipose tissue of skeletal muscle and the brain), and constitute approximately 35% of essential amino acids in mammals (Bifari & Nisoli, 2017; Neinast et al., 2019). Leu has been suggested as the most potent amino acid to activate mTORC1 (Avruch et al., 2009; Kiffin, 2010; Morris, 2016; Pinkerton & Barrientos, 2023). It plays important roles in the regulation of protein synthesis, energy metabolism, and immune functions (Rehman et al., 2023). Furthermore, BCAAs levels are often elevated in individuals with obesity and type 2 diabetes, likely contributing to disruptions of mTOR signaling in these metabolic diseases (Torres et al., 2023). The underlying mechanism for mTORC1 activation is Leu's direct binding to Sestrin2, a negative regulator of mTORC1 (Wolfson et al., 2016). In essence, Sestrin2 serves as a Leu sensor for mTORC1 signaling and plays a key role in cellular metabolism and maintaining homeostasis (J.-K. Liu, 2022; Wolfson et al., 2016). Importantly, Sestrin2 is a stress response protein that enhances autophagy, possesses potent antioxidant effects, inhibits inflammation, and has protective roles in metabolic diseases (J.-K. Liu, 2022; Seale et al., 2024). The above-described roles of BCAAs, particularly Leu, along with activation of mTORC1 and inactivation of Sestrin2, underscore the important adaptive role BCAAs, Sestrin2, mTORC1, and autophagy play during starvation.

Integrated molecular mechanisms of energy homeostasis

The adaptive roles that the above molecules, hormones, and metabolic pathways play to stimulate autophagy and inhibit mTORC1 and translation during starvation are listed in Table 1. Our work describing the biosynthesis, metabolism, and nutrient-sensing interactions of these pathways is expected to enhance the comprehension of cellular adaptation and energy homeostasis during starvation.

Table 1 The signaling role of various molecules that result in different cellular metabolic outcomes during starvation.

Molecule	Activity or levels	Proposed metabolic outcome	Key studies
Acetyl-CoA	↓	↑Autophagy	(Mariño, Pietrocola, Madeo, et al., 2014; Pietrocola et al., 2015; Schroeder et al., 2014; Zhou et al., 2019)
		↓EP300	(Mariño, Pietrocola, Eisenberg, et al., 2014)
		↓mTORC1	(Mariño, Pietrocola, Madeo, et al., 2014)
Amino acids	↓	↑Autophagy	(Albaugh et al., 2017; Changou et al., 2014; Kelly & Pearce, 2020; Lauinger & Kaiser, 2021; Neves et al., 2015; Z. Wu et al., 2015; Zhou et al., 2019)
		↑Apoptosis	(Albaugh et al., 2017; Z. Wu et al., 2015; Zhou et al., 2019)
		↓mTORC1	(Bröer & Bröer, 2017; Gu et al., 2017; Hong et al., 2024; Kelly & Pearce, 2020; Li et al., 2023; Mariño, Pietrocola, Madeo, et al., 2014; Morris, 2016; Pinkerton & Barrientos, 2023; Ray et al., 2015; Viola & Bronte, 2007)
		↓Translation	(Torres et al., 2023)
		↓45S pre-rRNA	(Munro et al., 1975)

		↓S6K	(Chotechuang, 2010; Morris, 2016)
		↑AZ	(Ray et al., 2012)
		↑Sestrin2	(Wolfson et al., 2016)
		↓eIF-2B	(Gross & Rubino, 1989)
		↑4E-BP1	(Ray et al., 2012)
Carbohydrates (particularly glucose)	↓	↑Autophagy ↓mTORC1	(Kiffin, 2010; Neves et al., 2015) (Blagih, 2015; Lee et al., 2009; Li et al., 2023; Metur & Klionsky, 2024; Saxton & Sabatini, 2017)
Glucagon	↑	↑Autophagy	(Kiffin, 2010; Ruan et al., 2017; Shen & Czaja, 2019)
		↓mTORC1	(Naito et al., 2013)
Hypusinated eIF5A	↑	↑Autophagy	(Hofer, Daskalaki, Bergmann, et al., 2024)
Insulin	↓	↑Autophagy	(Kiffin, 2010; Naito et al., 2013; Shen & Czaja, 2019)
mTORC1	↓	↑Autophagy	(J.-K. Liu, 2022; Metur & Klionsky, 2024; Pinkerton & Barrientos, 2023; Saxton & Sabatini, 2017; Settembre et al., 2012)
		↑Gluconeogenesis	(Saxton & Sabatini, 2017)
		↓Translation	(Bröer & Bröer, 2017)
		↓5S rRNA and tRNA	(Kantidakis et al., 2010; Laplante & Sabatini, 2012)
		↑Lifespan	(J.-K. Liu, 2022)
Ornithine δ-aminotransferase	↓	↑Ornithine	(Lenaerts et al., 2006)
Ornithine transcarbamylase	↓	↑Polyamines	(Weber et al., 1972)
Polyamines	↓	↑ODC	(Schertel & Eichler, 1991)
		↓eIF-2B	(Gross & Rubino, 1989)
SAM	↓	↑Autophagy; ↓mTORC1	(Ouyang et al., 2020)
		↑SAMTOR	(Gu et al., 2017)
Spermidine	↑	↑Autophagy; ↑Lifespan	(Hofer, Daskalaki, Bergmann, et al., 2024)
Urea	↑	↓mTORC1	(H. Wang et al., 2019)

AZ: antizyme; EP300: E1A-associated protein p300; eIF-2B: eukaryotic initiation factor-2B; eIF5A: eukaryotic initiation factor 5A; mTORC1: mammalian target of rapamycin complex 1; ODC: Ornithine decarboxylase; rRNA: ribosomal RNA; SAM: S-adenosylmethionine; tRNA: transfer RNA; S6K: ribosomal protein 6 kinase; Upward arrow indicates "increase" and downward arrow indicates "reduction" in the molecular levels or metabolic outcomes during starvation.

Information presented in the above table demonstrates the complexity of a multifaceted adaptation process of mammalian cells during starvation. The synchronized interplay between lack of essential molecules (amino acids, carbohydrates, polyamines, SAM), hormones (glucagon, insulin), proteins (metabolic enzymes, eIF5A, ribosomal proteins) and biochemical processes (mTORC1, translation, autophagy) reveal that mammalian cells are evolutionarily developed and equipped to maintain homeostasis under starvation. To mobilize a cascade of pathways and molecules to respond to starvation is a complex, yet coordinated survival unit, that operates under the sophisticated "command and control" center (CNS and endocrine system) in mammals. While table 1 summarizes key results, it is non-comprehensive. Continued research studies are essential to map additional or precise molecular pathways that are involved in adaptive mechanisms during starvation.

Discussion

Pre-clinical and clinical studies in the last decades have suggested a relationship between different forms of overlapping, but sometimes distinct effects of fasting and caloric restriction (CR) have been observed on physiology, health and cell biology (Koppold et al., 2024). Most strikingly, CR and fasting have been suggested to delay cellular aging processes and the progression of multiple age-associated diseases (Di Francesco et al., 2018; Mattson et al., 2018). Several studies across different populations indicate that practicing CR reduces the mortality rate of humans (Kagawa, 1978; Most et al., 2017; Strøm et al., 1951; Willcox et al., 2007). However, the exact molecular mechanisms underlying these observations in humans are not fully understood. Mammals have evolutionary conserved multiprotein complexes to rapidly sense energy, adapt, and recruit a cascade of signaling molecules to survive starvation. In this review study, we have explored existing literature and applied a reconnaissance strategy to shed more light on the interplay between starvation, polyamines (and their precursors), autophagy, and protein synthesis in mammalian cellular adaptation. Among several metabolic pathways that are affected during starvation, metabolism of polyamines and biosynthesis of proteins, including their adaptive mechanisms in mTORC1 signaling and autophagy, have played a central role in our study and are discussed in the following sections.

Regulation of polyamine metabolism during starvation

The functions of polyamines have been extensively studied in tumors, aging, and immunity, and an interest to explore the role of polyamine biosynthesis in clinical translational research has steadily grown over recent years. There are several enzymes that control polyamine biosynthesis and a broad range of molecules that are involved throughout polyamines metabolism. Recently, acute bouts of fasting were shown to temporarily increase Spd levels and hypusinated eIF5A suggesting a more complex interplay between starvation and polyamine biosynthesis (Hofer, Daskalaki, Bergmann, et al., 2024). Since hypusinated eIF5A enhances and controls translation of TFEB, at least in B cells (H. Zhang et al., 2019), this mechanism may represent an important temporal window in ensuring sufficient lysosomal biogenesis to support sustained autophagy during fasting. Interestingly, Spm and, to a lesser extent, Spd, has been shown to stimulate mTORC1 activity in the absence of amino acids (Ray et al., 2015). This also supports the notion that temporal increases in polyamine levels during starvation have stimulatory effects on mTORC1 through an as-yet-unknown adaptive mechanism. This is highlighted by findings that ODC1-deficient yeast cells have a delayed mTORC1 shut-off upon amino acid starvation (Hofer, Daskalaki, Bergmann, et al., 2024). Further research is necessary to understand how polyamines regulate mTORC1 during amino acid starvation, which may be crucial for understanding the simultaneous occurrence of high rates of autophagy, mTORC1 activity, and translation in many tumor types. While the autophagy regulatory mechanism is mediated by eIF5A, studies are still needed to establish if the translational control of TFEB by hypusinated eIF5A is consistent across different mammalian cells. Additionally, it remains to be determined whether eIF5A-mediated stimulation of autophagic flux affects mTORC1 signaling during starvation.

Our review study revealed contrasting data regarding the production of polyamines and expression or activity of ODC during starvation. In a study in which preweaned rats were investigated, starvation at postnatal day 12 resulted in increased levels of corticosterone and enhanced intestinal expression of ODC, ultimately resulting in increased polyamine content (Nsi-Emvo et al., 1996). Similarly, ODC activity was shown to be higher in the liver of arginine-starved rats than in control rats (Schertel & Eichler, 1991). Conversely, other studies found that starvation led to a marked decrease in ODC activity, including liver of starved rats (Conover et al., 1980; Domschke & Söling, 1973; Eloranta & Raina, 1977). Similarly, ODC activity and polyamines levels were reduced in the small intestinal mucosa of rats that were starved for 48 hours (Yang et al., 1999). Given the use of different cell types and lengths of starvation, a universal temporal pattern of ODC expression and activity is lacking during starvation. Further studies in mammals are needed to elucidate the role of ODC, and ultimately polyamine metabolism during starvation. Based on recent studies, it's largely proven that starvation increases the biosynthesis of Spd. Two earlier studies, however, demonstrated that during 24 and 56 hours of starvation, the liver of lactating rats (Brosnan et al., 1983) and rats liver (Seiler et al., 1981), respectively, produced lower levels of Spd. It is unclear whether the marked decrease in liver weights and the physiology of the mammary glands in lactating rats played a role in the levels of Spd in these data.

Regulation of protein synthesis during starvation

The translational apparatus plays a central role in synthesizing proteins required for cellular functions and structures (Fedry et al., 2024; Jia et al., 2024). Translation is one of the most energetically costly pathways in both prokaryotic and eukaryotic organisms. It is estimated that approximately 30% of total cellular ATP energy is used during translation in mammals (Buttgereit & Brand, 1995). During starvation, the cell activates autophagy, a crucial

protective mechanism to resist the nutrient threat. This process involves the degradation of cellular components within the lysosome, liberating molecules like amino acids (Kelly & Pearce, 2020). These recycled amino acids then serve as a vital nutrient bank, sustaining essential intracellular metabolic pathways and promoting cellular survival and energy homeostasis. Therefore, during starvation and alongside autophagy, a tightly regulated inhibition of translation is required to ensure efficient cellular energy conservation.

Translation is one of the main targets of mTORC1 signaling. Our review study supports the essential role of mTORC1 as a major hub in the regulation of translation. mTORC1 enhances ribosomal biogenesis, phosphorylation of S6K, and activation of translation initiation factor, eIF4E (Bröer & Bröer, 2017; Chotechuang, 2010; Christian, 2002; Hong et al., 2024; Laplante & Sabatini, 2012; Li et al., 2023; Pinkerton & Barrientos, 2023; Rousseau et al., 1996; Russell et al., 2014). Since amino acids are not only involved in protein synthesis but also in being oxidized to produce energy, the activation of mTORC1 is tightly associated with changes in the plasma levels of amino acids (Saxton & Sabatini, 2017). When plasma levels of amino acids are high, mTORC1 is activated to promote translation through its stimulatory effect on the eIF4E and S6K. Conversely, amino acid depletion inactivates mTORC1, leading to the repression of eIF4E-dependent translation and the induction of proteolysis through autophagy (Bröer & Bröer, 2017). Altogether, these data suggest that the cell's most significant adaptation during starvation is the inhibition of mTORC1 to downregulate the translational apparatus and conserve cellular energy.

Regulation of autophagy and mTORC1 during starvation

Autophagy and the mTORC1 signaling pathway are two opposing processes in mammalian cellular metabolism that are regulated by the levels of nutrients and cellular energy. Autophagy drives catabolism, while mTORC1 promotes anabolism. The inverse relationship between autophagy and mTORC1 serves our cells to sustain cellular homeostasis during starvation. Essentially, when nutrients are limited, our cells mobilize a series of molecules and pathways to downregulate mTORC1 and upregulate autophagy to promote energy conservation and bolster cellular resistance against stressful conditions such as starvation. As highlighted earlier, there is a growing body of evidence that dysregulations of one or both pathways contribute to a variety of human diseases, including aging. Aging is recognized as a major risk factor for the development of cancer and metabolic disorders such as obesity and type 2 diabetes (Cornu et al., 2013). In addition, aging significantly decreases the total body protein synthesis in humans (Bifari & Nisoli, 2017). Overall, regulation of autophagy and mTORC1 and their impact on translation highlights the imperative and evolutionary roles that they have played in the survival of mammalian cells.

A simple holistic view that indicates that there is an adaptive crosstalk between autophagy, mTORC1, and translation is shown in Fig.5. Our review study indicates that starvation changes the levels of at least 12 molecules or pathways to directly or indirectly inhibit mTORC1 to induce autophagy. While eIF5A, glucagon, sestrin2, Spd, TFEB, and urea levels increase, the levels of acetyl-CoA, amino acids, EP30, glucose, insulin and SAM decrease during starvation in order to inhibit mTORC1 or induce autophagy (Fig. 5). It is likely that these molecules and pathways are uniquely positioned to exert their cellular impact on autophagy and mTORC1 and are not substituted by each other or by other molecules or pathways. The full interplay between autophagy and mTORC1 is complex and remains to be fully established. As a result, it is important to emphasize here that the above number of molecules and pathways shown in Table 1 or Fig. 5 is non-exhaustive and further studies are needed to identify other underlying molecular mechanisms that support cellular survival during starvation. Fig 5 summarizes that while mTORC1 and translation are inhibited, autophagy is induced to conserve and replenish energy reserves to ensure an adequate pool of nutrients is available to assist the mammalian cell in surviving the threat of starvation.

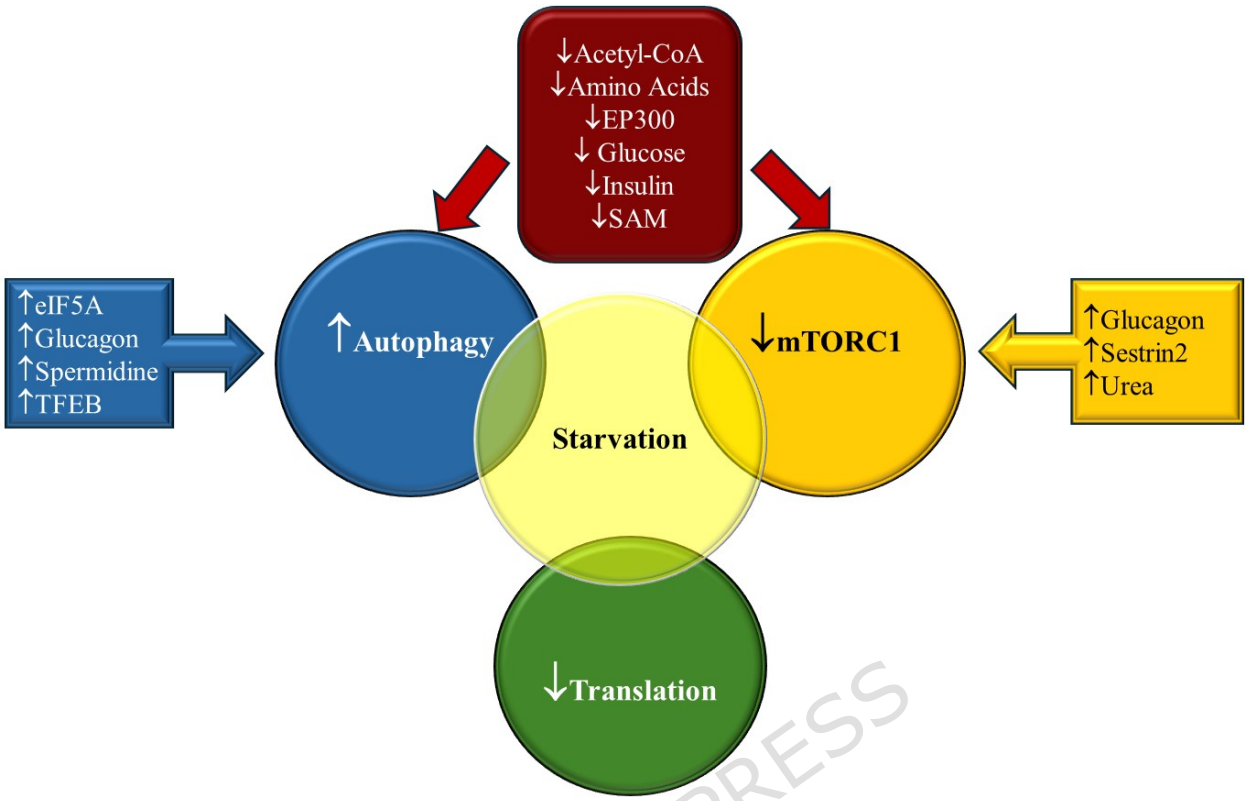

Fig. 5 A simple holistic view of three cellular processes, autophagy, mTORC1, and translation that, in an adaptive and integrated manner, are affected during starvation in mammals. The effects of cellular molecules that change during starvation and influence mTORC1 or autophagy (or both) in mammalian cells are illustrated. Upward arrows indicate "increase" and downward arrows indicate "reduction" in the molecular levels or metabolic outcomes during starvation. EP300: E1A-associated protein p300; eIF5A, eukaryotic initiation factor; mTORC1, mammalian target of rapamycin complex 1; SAM, S-adenosylmethionine; TFEB, transcription factor EB

Strengths and Limitations

This review study has several strengths. One is that we used four different databases to ensure that we have reviewed as many articles as possible to address the objective of our study. Another strength is that at least two authors reviewed all abstracts twice to ensure that relevant information was included in our study. In order to minimize bias in our review analysis, we included contrasting data with a hope that future studies will shed more light on different results. Another strength is that we mapped a diverse set of molecules or pathways to starvation. Lastly, our findings can serve as an educational resource to educate students to maximize their understanding of the adaptive roles that cellular molecules and pathways play during starvation in mammals.

A few limitations exist. Non-English language studies were excluded from our review, representing a potential limitation in the comprehensiveness of our findings. Furthermore, our review, although focused on mammalian systems, was complicated by the presence of organ- and cell-specific variations and different lengths of starvation (including *in vitro* cell culture systems), making the deduction of a universal model challenging.

Conclusions

Autophagy is a key cellular adaptive process that, among other roles, recycles cellular cargo to sustain energy homeostasis during starvation. The growth- and translation-promoting kinase mTORC1 centrally links fluctuations in metabolic and nutrient availability to the regulation of autophagy. Sensing nutrient availability and coordinating autophagy regulation, mTORC1 activity, and ultimately translation processes involve a cascade of multiple cellular molecules and pathways. During starvation, polyamine anabolism increases levels of Spd followed by activation of hypusinated eIF5A and translation of TFEB to promote autophagy in some cell types, presenting an example of adaptive mTORC1-autophagy-translation interplay. Emerging evidence indicates that polyamines take part in an

adaptive crosstalk that sustains energy homeostasis during starvation in mammals. In addition, starvation increases glucagon, urea and Sestrin2 resulting in the inhibition of mTORC1 which ultimately results in the induction of autophagy. Similarly, reduced levels of acetyl-CoAs, amino acids, EP300, glucose, insulin, and SAM suppresses mTORC1 and enhances autophagy. Inhibition of mTORC1 results in the reduction of ribosome biogenesis and translation factors that ultimately lead to the suppression of the translational apparatus. While the inhibition of translation conserves a significant amount of cellular energy, the autophagy process assists the cell in meeting cellular energy needs during starvation. In sum, we illustrated how different nutrients and nutrient-sensing pathways are mobilized to promote an adaptive crosstalk between autophagy, mTORC1, and translation to ensure that the mammalian cell survives the threat of starvation. Yet, more studies are required to explore the adaptive roles signaling molecules play in translation, mTORC1, and autophagy which ultimately may offer insights into possible therapeutic targets for uncoupling these mechanisms in treating various disorders.

Statements and Declarations

Funding: No funding was received for conducting this study.
Conflicts of Interest: The authors have no relevant financial or non-financial interests to disclose.

References

Albaugh, V. L., Pinzon□Guzman, C., & Barbul, A. (2017). Arginine—Dual roles as an onconutrient and immunonutrient. *Journal of Surgical Oncology*, *115*(3), 273–280. https://doi.org/10.1002/jso.24490

Alexandrou, C., Al-Aqbi, S. S., Higgins, J. A., Boyle, W., Karmokar, A., Andreadi, C., Luo, J.-L., Moore, D. A., Viskaduraki, M., Blades, M., Murray, G. I., Howells, L. M., Thomas, A., Brown, K., Cheng, P. N., & Rufini, A. (2018). Sensitivity of Colorectal Cancer to Arginine Deprivation Therapy is Shaped by Differential Expression of Urea Cycle Enzymes. *Scientific Reports*, *8*(1), 12096. https://doi.org/10.1038/s41598-018-30591-7

Alsaleh, G., Panse, I., Swadling, L., Zhang, H., Richter, F. C., Meyer, A., Lord, J., Barnes, E., Klenerman, P., Green, C., & Simon, A. K. (2020). Autophagy in T cells from aged donors is maintained by spermidine and correlates with function and vaccine responses. *eLife*, *9*, e57950. https://doi.org/10.7554/eLife.57950

Amorim, T., Khiyami, A., Latif, T., & Fazeli, P. K. (2023). Neuroendocrine adaptations to starvation. *Psychoneuroendocrinology*, *157*, 106365. https://doi.org/10.1016/j.psyneuen.2023.106365

Aromataris, E., & Riitano, D. (2014). Systematic Reviews: Constructing a Search Strategy and Searching for Evidence. *AJN, American Journal of Nursing*, *114*(5), 49–56. https://doi.org/10.1097/01.NAJ.0000446779.99522.f6

Ast, T. (1995). *Purification, characterisation and inhibition of methionine synthase from rat liver* [Dissertation, University College London]. https://discovery.ucl.ac.uk/id/eprint/10102673

Avruch, J., Long, X., Ortiz-Vega, S., Rapley, J., Papageorgiou, A., & Dai, N. (2009). Amino acid regulation of TOR complex 1. *American Journal of Physiology-Endocrinology and Metabolism*, *296*(4), E592–E602. https://doi.org/10.1152/ajpendo.90645.2008

Bergamini, E., Cavallini, G., Donati, A., & Gori, Z. (2007). The Role of Autophagy in Aging: Its Essential Part in the Anti□Aging Mechanism of Caloric Restriction. *Annals of the New York Academy of Sciences*, *1114*(1), 69–78. https://doi.org/10.1196/annals.1396.020

Bhowmick, T., Biswas, S., & Mukherjee, A. (2024). Cellular response during cellular starvation: A battle for cellular survivability. *Cell Biochemistry and Function*, *42*(5), e4101. https://doi.org/10.1002/cbf.4101

Bifari, F., & Nisoli, E. (2017). Branched□chain amino acids differently modulate catabolic and anabolic states in mammals: A pharmacological point of view. *British Journal of Pharmacology*, *174*(11), 1366–1377. https://doi.org/10.1111/bph.13624

Blagih, J. (2015). *The role of metabolic regulators, LKB1, AMPK, and mTORC1, in T cell function, metabolism and immunity. McGill University Montreal, Quebec, Canada.* [Dissertation, McGill University Montreal, Quebec, Canada.]. https://escholarship.mcgill.ca/concern/theses/8s45qc65p

Bröer, S., & Bröer, A. (2017). Amino acid homeostasis and signalling in mammalian cells and organisms. *Biochemical Journal*, *474*(12), 1935–1963. https://doi.org/10.1042/BCJ20160822

Brosnan, M. E., Farrell, R., Wilansky, H., & Williamson, D. H. (1983). Effect of starvation and refeeding on polyamine concentrations and ornithine decarboxylase antizyme in mammary gland of lactating rats. *Biochemical Journal*, *212*(1), 149–153. https://doi.org/10.1042/bj2120149

Buttgereit, F., & Brand, M. D. (1995). A hierarchy of ATP-consuming processes in mammalian cells. *Biochemical Journal*, *312*(1), 163–167. https://doi.org/10.1042/bj3120163

Cano, V. S. P., Jeon, G. A., Johansson, H. E., Henderson, C. A., Park, J., Valentini, S. R., Hershey, J. W. B., & Park, M. H. (2008). Mutational analyses of human eIF5A□1 – identification of amino acid residues critical for eIF5A activity and hypusine modification. *The FEBS Journal*, *275*(1), 44–58. https://doi.org/10.1111/j.1742-4658.2007.06172.x

Caregaro, L., Di Pascoli, L., Favaro, A., Nardi, M., & Santonastaso, P. (2005). Sodium depletion and hemoconcentration: Overlooked complications in patients with anorexia nervosa? *Nutrition*, *21*(4), 438–445. https://doi.org/10.1016/j.nut.2004.08.022

Carter, N. S., Kawasaki, Y., Nahata, S. S., Elikaee, S., Rajab, S., Salam, L., Alabdulal, M. Y., Broessel, K. K., Foroghi, F., Abbas, A., Poormohamadian, R., & Roberts, S. C. (2022). Polyamine Metabolism in Leishmania Parasites: A Promising Therapeutic Target. *Medical Sciences*, *10*(2), 24. https://doi.org/10.3390/medsci10020024

Changou, C. A., Chen, Y.-R., Xing, L., Yen, Y., Chuang, F. Y. S., Cheng, R. H., Bold, R. J., Ann, D. K., & Kung, H.-J. (2014). Arginine starvation-associated atypical cellular death involves mitochondrial dysfunction, nuclear DNA leakage, and chromatin autophagy. *Proceedings of the National Academy of Sciences*, *111*(39), 14147–14152. https://doi.org/10.1073/pnas.1404171111

Childs, A. C., Mehta, D. J., & Gerner, E. W. (2003). Polyamine-dependent gene expression. *Cellular and Molecular Life Sciences (CMLS)*, *60*(7), 1394–1406. https://doi.org/10.1007/s00018-003-2332-4

Chisari, A., Golán, I., Campisano, S., Gélabert, C., Moustakas, A., Sancho, P., & Caja, L. (2021). Glucose and Amino Acid Metabolic Dependencies Linked to Stemness and Metastasis in Different Aggressive Cancer Types. *Frontiers in Pharmacology*, *12*, 723798. https://doi.org/10.3389/fphar.2021.723798

Chotechuang, Nattida. (2010). *The role of amino acids in liver protein metabolism under a high protein diet: Identification of amino acids signal and associated transduction pathways.* [Dissertation, ParisTech Paris Institute of Technology]. https://pastel.hal.science/pastel-00610998v1

Christian, J. F. (2002). *Transcriptional regulation of 4E -BP1 by polyamines* [Dissertation, Brody School of Medicine at East Carolina University]. https://pacificu.idm.oclc.org/login?url=https://www.proquest.com/dissertations-theses/transcriptional-regulation-4e-bp1-polyamines/docview/276005788/se-2

Codoñer-Franch, P., Tavárez-Alonso, S., Murria-Estal, R., Herrera-Martín, G., & Alonso-Iglesias, E. (2011). Polyamines Are Increased in Obese Children and Are Related to Markers of Oxidative/Nitrosative Stress and Angiogenesis. *The Journal of Clinical Endocrinology & Metabolism*, *96*(9), 2821–2825. https://doi.org/10.1210/jc.2011-0531

Conover, C. A., Rozovski, S. J., Belur, E. R., Aoki, T. T., & Ruderman, N. B. (1980). Ornithine decarboxylase activity in insulin-deficient states. *Biochemical Journal*, *192*(2), 725–732. https://doi.org/10.1042/bj1920725

Cornu, M., Albert, V., & Hall, M. N. (2013). mTOR in aging, metabolism, and cancer. *Current Opinion in Genetics & Development*, *23*(1), 53–62. https://doi.org/10.1016/j.gde.2012.12.005

Dazert, E., & Hall, M. N. (2011). mTOR signaling in disease. *Current Opinion in Cell Biology*, *23*(6), 744–755. https://doi.org/10.1016/j.ceb.2011.09.003

Del Roso, A. (2003). Ageing-related changes in the in vivo function of rat liver macroautophagy and proteolysis. *Experimental Gerontology*, *38*(5), 519–527. https://doi.org/10.1016/S0531-5565(03)00002-0

Di Francesco, A., Di Germanio, C., Bernier, M., & De Cabo, R. (2018). A time to fast. *Science*, *362*(6416), 770–775. https://doi.org/10.1126/science.aau2095

Domschke, S., & Söling, H. (1973). Polyamine Metabolism in Rat Liver: Effect of Starvation and Refeeding. *Hormone and Metabolic Research*, *5*(02), 97–101. https://doi.org/10.1055/s-0028-1093971

Eisenberg, T., Abdellatif, M., Schroeder, S., Primessnig, U., Stekovic, S., Pendl, T., Harger, A., Schipke, J., Zimmermann, A., Schmidt, A., Tong, M., Ruckenstuhl, C., Dammbrueck, C., Gross, A. S., Herbst, V., Magnes, C., Trausinger, G., Narath, S., Meinitzer, A., … Madeo, F. (2016). Cardioprotection and lifespan extension by the natural polyamine spermidine. *Nature Medicine*, *22*(12), 1428–1438. https://doi.org/10.1038/nm.4222

Eisenberg, T., Knauer, H., Schauer, A., Büttner, S., Ruckenstuhl, C., Carmona-Gutierrez, D., Ring, J., Schroeder, S., Magnes, C., Antonacci, L., Fussi, H., Deszcz, L., Hartl, R., Schraml, E., Criollo, A., Megalou, E., Weiskopf, D., Laun, P., Heeren, G., … Madeo, F. (2009). Induction of autophagy by spermidine promotes longevity. *Nature Cell Biology*, *11*(11), 1305–1314. https://doi.org/10.1038/ncb1975

Eloranta, T. O., & Raina, A. M. (1977). *S* -Adenosylmethionine metabolism and its relation to polyamine synthesis in rat liver. Effect of nutritional state, adrenal function, some drugs and partial hepatectomy. *Biochemical Journal*, *168*(2), 179–185. https://doi.org/10.1042/bj1680179

Emery, P. W. (2013). Amino acids: Metabolism. In *Encyclopedia of Human Nutrition* (pp. 72–78). Elsevier. https://doi.org/10.1016/B978-0-12-375083-9.00010-6

Fedry, J., Silva, J., Vanevic, M., Fronik, S., Mechulam, Y., Schmitt, E., Des Georges, A., Faller, W. J., & Förster, F. (2024). Visualization of translation reorganization upon persistent ribosome collision stress in mammalian cells. *Molecular Cell*, *84*(6), 1078-1089.e4. https://doi.org/10.1016/j.molcel.2024.01.015

Fîlfan, M., Sandu, R. E., Zăvăleanu, A. D., GreşiŢă, A., Glăvan, D. G., Olaru, D. G., & Popa-Wagner, A. (2017). Autophagy in aging and disease. *Romanian Journal of Morphology and Embryology = Revue Roumaine De Morphologie Et Embryologie*, *58*(1), 27–31.

Fox, M. K. (2022). *The Effects of Arginine on Gene Expression in Bovine Mammary and Longissimus Dorsi Tissues. The University of Guelph.* [Dissertation, The University of Guelph]. https://hdl.handle.net/10214/26978

Fyfe, J. J., Bishop, D. J., Bartlett, J. D., Hanson, E. D., Anderson, M. J., Garnham, A. P., & Stepto, N. K. (2018). Enhanced skeletal muscle ribosome biogenesis, yet attenuated mTORC1 and ribosome biogenesis-related signalling, following short-term concurrent versus single-mode resistance training. *Scientific Reports*, *8*(1), 560. https://doi.org/10.1038/s41598-017-18887-6

Ghosh, I., Sankhe, R., Mudgal, J., Arora, D., & Nampoothiri, M. (2020). Spermidine, an autophagy inducer, as a therapeutic strategy in neurological disorders. *Neuropeptides*, *83*, 102083. https://doi.org/10.1016/j.npep.2020.102083

Ginguay, A., Cynober, L., Curis, E., & Nicolis, I. (2017). Ornithine Aminotransferase, an Important Glutamate-Metabolizing Enzyme at the Crossroads of Multiple Metabolic Pathways. *Biology*, *6*(1), 18. https://doi.org/10.3390/biology6010018

Glick, D., Barth, S., & Macleod, K. F. (2010). Autophagy: Cellular and molecular mechanisms. *The Journal of Pathology*, *221*(1), 3–12. https://doi.org/10.1002/path.2697

Gomes, A. P., Schild, T., & Blenis, J. (2017). Adding Polyamine Metabolism to the mTORC1 Toolkit in Cell Growth and Cancer. *Developmental Cell*, *42*(2), 112–114. https://doi.org/10.1016/j.devcel.2017.07.004

Grohmann, U., & Bronte, V. (2010). Control of immune response by amino acid metabolism. *Immunological Reviews*, *236*(1), 243–264. https://doi.org/10.1111/j.1600-065X.2010.00915.x

Grohmann, U., Mondanelli, G., Belladonna, M. L., Orabona, C., Pallotta, M. T., Iacono, A., Puccetti, P., & Volpi, C. (2017). Amino-acid sensing and degrading pathways in immune regulation. *Cytokine & Growth Factor Reviews*, *35*, 37–45. https://doi.org/10.1016/j.cytogfr.2017.05.004

Gross, M., & Rubino, M. S. (1989). Regulation of eukaryotic initiation factor-2B activity by polyamines and amino acid starvation in rabbit reticulocyte lysate. *The Journal of Biological Chemistry*, *264*(36), 21879–21884.

Gu, X., Orozco, J. M., Saxton, R. A., Condon, K. J., Liu, G. Y., Krawczyk, P. A., Scaria, S. M., Harper, J. W., Gygi, S. P., & Sabatini, D. M. (2017). SAMTOR is an *S* -adenosylmethionine sensor for the mTORC1 pathway. *Science*, *358*(6364), 813–818. https://doi.org/10.1126/science.aao3265

Hofer, S. J., Carmona□Gutierrez, D., Mueller, M. I., & Madeo, F. (2022). The ups and downs of caloric restriction and fasting: From molecular effects to clinical application. *EMBO Molecular Medicine*, *14*(1), e14418. https://doi.org/10.15252/emmm.202114418

Hofer, S. J., Daskalaki, I., Abdellatif, M., Stelzl, U., Sedej, S., Tavernarakis, N., Kroemer, G., & Madeo, F. (2024). A surge in endogenous spermidine is essential for rapamycin-induced autophagy and longevity. *Autophagy*, *20*(12), 2824–2826. https://doi.org/10.1080/15548627.2024.2396793

Hofer, S. J., Daskalaki, I., Bergmann, M., Friščić, J., Zimmermann, A., Mueller, M. I., Abdellatif, M., Nicastro, R., Masser, S., Durand, S., Nartey, A., Waltenstorfer, M., Enzenhofer, S., Faimann, I., Gschiel, V., Bajaj, T., Niemeyer, C., Gkikas, I., Pein, L., … Madeo, F. (2024). Spermidine is essential for fasting-mediated autophagy and longevity. *Nature Cell Biology*, *26*(9), 1571–1584. https://doi.org/10.1038/s41556-024-01468-x

Holbert, C. E., Dunworth, M., Foley, J. R., Dunston, T. T., Stewart, T. M., & Casero, R. A. (2020). Autophagy induction by exogenous polyamines is an artifact of bovine serum amine oxidase activity in culture serum. *Journal of Biological Chemistry*, *295*(27), 9061–9068. https://doi.org/10.1074/jbc.RA120.013867

Hong, J., Liu, W., Xiao, X., Gajendran, B., & Ben-David, Y. (2024). Targeting pivotal amino acids metabolism for treatment of leukemia. *Heliyon*, *10*(23), e40492. https://doi.org/10.1016/j.heliyon.2024.e40492

Hu, Q., Dai, J., Zhang, Z., Yu, H., Zhang, J., Zhu, X., Qin, Y., Zhang, L., & Zhang, P. (2023). ASS1-Mediated Reductive Carboxylation of Cytosolic Glutamine Confers Ferroptosis Resistance in Cancer Cells. *Cancer Research*, *83*(10), 1646–1665. https://doi.org/10.1158/0008-5472.CAN-22-1999

Huang, S. (2020). mTOR Signaling in Metabolism and Cancer. *Cells*, *9*(10), 2278. https://doi.org/10.3390/cells9102278

Hukelmann, J. L., Anderson, K. E., Sinclair, L. V., Grzes, K. M., Murillo, A. B., Hawkins, P. T., Stephens, L. R., Lamond, A. I., & Cantrell, D. A. (2016). The cytotoxic T cell proteome and its shaping by the kinase mTOR. *Nature Immunology*, *17*(1), 104–112. https://doi.org/10.1038/ni.3314

Ichimiya, T., Yamakawa, T., Hirano, T., Yokoyama, Y., Hayashi, Y., Hirayama, D., Wagatsuma, K., Itoi, T., & Nakase, H. (2020). Autophagy and Autophagy-Related Diseases: A Review. *International Journal of Molecular Sciences*, *21*(23), 8974. https://doi.org/10.3390/ijms21238974

Igarashi, K., & Kashiwagi, K. (2011). Characterization of Genes for Polyamine Modulon. In A. E. Pegg & R. A. Casero, (Eds.), *Polyamines* (Vol. 720, pp. 51–65). Humana Press. https://doi.org/10.1007/978-1-61779-034-8_3

Ivanov, I. P., & Atkins, J. F. (2007). Ribosomal frameshifting in decoding antizyme mRNAs from yeast and protists to humans: Close to 300 cases reveal remarkable diversity despite underlying conservation. *Nucleic Acids Research*, *35*(6), 1842–1858. https://doi.org/10.1093/nar/gkm035

Ivanovski, O., Szumilak, D., Nguyen-Khoa, T., Ruellan, N., Phan, O., Lacour, B., Descamps-Latscha, B., Dreeke, T. B., & Massy, Z. A. (2005). The antioxidant N-acetylcysteine prevents accelerated atherosclerosis in uremic apolipoprotein E knockout mice. *Kidney International*, *67*(6), 2288–2294. https://doi.org/10.1111/j.1523-1755.2005.00332.x

Jia, X., He, X., Huang, C., Li, J., Dong, Z., & Liu, K. (2024). Protein translation: Biological processes and therapeutic strategies for human diseases. *Signal Transduction and Targeted Therapy*, *9*(1), 44. https://doi.org/10.1038/s41392-024-01749-9

Kagawa, Y. (1978). Impact of westernization on the nutrition of Japanese: Changes in physique, cancer, longevity and centenarians. *Preventive Medicine*, *7*(2), 205–217. https://doi.org/10.1016/0091-7435(78)90246-3

Kantidakis, T., Ramsbottom, B. A., Birch, J. L., Dowding, S. N., & White, R. J. (2010). mTOR associates with TFIIIC, is found at tRNA and 5S rRNA genes, and targets their repressor Maf1. *Proceedings of the National Academy of Sciences*, *107*(26), 11823–11828. https://doi.org/10.1073/pnas.1005188107

Karimi, R., Cleven, A., Elbarbry, F., & Hoang, H. (2021). The Impact of Fasting on Major Metabolic Pathways of Macronutrients and Pharmacokinetics Steps of Drugs. *European Journal of Drug Metabolism and Pharmacokinetics*, *46*(1), 25–39. https://doi.org/10.1007/s13318-020-00656-y

Karimi, R., Yanovich, A., Elbarbry, F., & Cleven, A. (2024). Adaptive Effects of Endocrine Hormones on Metabolism of Macronutrients during Fasting and Starvation: A Scoping Review. *Metabolites*, *14*(6), 336. https://doi.org/10.3390/metabo14060336

Kaushik, S., Tasset, I., Arias, E., Pampliega, O., Wong, E., Martinez-Vicente, M., & Cuervo, A. M. (2021). Autophagy and the hallmarks of aging. *Ageing Research Reviews*, *72*, 101468. https://doi.org/10.1016/j.arr.2021.101468

Kelly, B., & Pearce, E. L. (2020). Amino Assets: How Amino Acids Support Immunity. *Cell Metabolism*, *32*(2), 154–175. https://doi.org/10.1016/j.cmet.2020.06.010

Kiffin, R. (2010). *The physiological effects of stress and aging on chaperone-mediated autophagy* [Dissertation, [Albert Einstein College of Medicine Yeshiva University New York].]. https://ezproxy.yu.edu/login?url=http://gateway.proquest.com/openurl?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:dissertation&res_dat=xri:pqm&rft_dat=xri:pqdiss:3446357

Kitada, M., Xu, J., Ogura, Y., Monno, I., & Koya, D. (2020). Mechanism of Activation of Mechanistic Target of Rapamycin Complex 1 by Methionine. *Frontiers in Cell and Developmental Biology*, *8*, 715. https://doi.org/10.3389/fcell.2020.00715

Klionsky, D. J., Petroni, G., Amaravadi, R. K., Baehrecke, E. H., Ballabio, A., Boya, P., Bravo□San Pedro, J. M., Cadwell, K., Cecconi, F., Choi, A. M. K., Choi, M. E., Chu, C. T., Codogno, P., Colombo, M. I., Cuervo, A. M., Deretic, V., Dikic, I., Elazar, Z., Eskelinen, E., … Pietrocola, F. (2021). Autophagy in major human diseases. *The EMBO Journal*, *40*(19), e108863. https://doi.org/10.15252/embj.2021108863

Koppold, D. A., Breinlinger, C., Hanslian, E., Kessler, C., Cramer, H., Khokhar, A. R., Peterson, C. M., Tinsley, G., Vernieri, C., Bloomer, R. J., Boschmann, M., Bragazzi, N. L., Brandhorst, S., Gabel, K., Goldhamer, A. C., Grajower, M. M., Harvie, M., Heilbronn, L., Horne, B. D., … Michalsen, A. (2024). International consensus on fasting terminology. *Cell Metabolism*, *36*(8), 1779-1794.e4. https://doi.org/10.1016/j.cmet.2024.06.013

Kroemer, G., Mariño, G., & Levine, B. (2010). Autophagy and the Integrated Stress Response. *Molecular Cell*, *40*(2), 280–293. https://doi.org/10.1016/j.molcel.2010.09.023

Lamming, D. W., & Sabatini, D. M. (2013). A Central Role for mTOR in Lipid Homeostasis. *Cell Metabolism*, *18*(4), 465–469. https://doi.org/10.1016/j.cmet.2013.08.002

Lampert, F., & Lau, B. (1976). Bone marrow hypoplasia in anorexia nervosa. *European Journal of Pediatrics*, *124*(1), 65–71. https://doi.org/10.1007/BF00452416

Laplante, M., & Sabatini, D. M. (2012). mTOR Signaling in Growth Control and Disease. *Cell*, *149*(2), 274–293. https://doi.org/10.1016/j.cell.2012.03.017

Lauinger, L., & Kaiser, P. (2021). Sensing and Signaling of Methionine Metabolism. *Metabolites*, *11*(2), 83. https://doi.org/10.3390/metabo11020083

Lee, M. N., Ha, S. H., Kim, J., Koh, A., Lee, C. S., Kim, J. H., Jeon, H., Kim, D.-H., Suh, P.-G., & Ryu, S. H. (2009). Glycolytic Flux Signals to mTOR through Glyceraldehyde-3-Phosphate Dehydrogenase-Mediated Regulation of Rheb. *Molecular and Cellular Biology*, *29*(14), 3991–4001. https://doi.org/10.1128/MCB.00165-09

Lei, Y., & Klionsky, D. J. (2023). Transcriptional regulation of autophagy and its implications in human disease. *Cell Death & Differentiation*, *30*(6), 1416–1429. https://doi.org/10.1038/s41418-023-01162-9

Lenaerts, K., Sokolović, M., Bouwman, F. G., Lamers, W. H., Mariman, E. C., & Renes, J. (2006). Starvation Induces Phase-Specific Changes in the Proteome of Mouse Small Intestine. *Journal of Proteome Research*, *5*(9), 2113–2122. https://doi.org/10.1021/pr060183+

Levine, B., Mizushima, N., & Virgin, H. W. (2011). Autophagy in immunity and inflammation. *Nature*, *469*(7330), 323–335. https://doi.org/10.1038/nature09782

Li, K., Wang, C., Wang, Y., Fu, L., & Zhang, N. (2023). Future foods, dietary factors and healthspan. *Journal of Future Foods*, *3*(2), 75–98. https://doi.org/10.1016/j.jfutfo.2022.12.001

Liu, J.-K. (2022). Antiaging agents: Safe interventions to slow aging and healthy life span extension. *Natural Products and Bioprospecting*, *12*(1), 18. https://doi.org/10.1007/s13659-022-00339-y

Liu, Y., & Gu, W. (2022). The complexity of p53-mediated metabolic regulation in tumor suppression. *Seminars in Cancer Biology*, *85*, 4–32. https://doi.org/10.1016/j.semcancer.2021.03.010

Lubas, M., Harder, L. M., Kumsta, C., Tiessen, I., Hansen, M., Andersen, J. S., Lund, A. H., & Frankel, L. B. (2018). EIF 5A is required for autophagy by mediating ATG 3 translation. *EMBO Reports*, *19*(6), e46072. https://doi.org/10.15252/embr.201846072

Madeo, F., Bauer, M. A., Carmona-Gutierrez, D., & Kroemer, G. (2019). Spermidine: A physiological autophagy inducer acting as an anti-aging vitamin in humans? *Autophagy*, *15*(1), 165–168. https://doi.org/10.1080/15548627.2018.1530929

Madeo, F., Eisenberg, T., Pietrocola, F., & Kroemer, G. (2018). Spermidine in health and disease. *Science*, *359*(6374), eaan2788. https://doi.org/10.1126/science.aan2788

Mandal, S., Mandal, A., Johansson, H. E., Orjalo, A. V., & Park, M. H. (2013). Depletion of cellular polyamines, spermidine and spermine, causes a total arrest in translation and growth in mammalian cells. *Proceedings of the National Academy of Sciences*, *110*(6), 2169–2174. https://doi.org/10.1073/pnas.1219002110

Mariño, G., Pietrocola, F., Eisenberg, T., Kong, Y., Malik, S. A., Andryushkova, A., Schroeder, S., Pendl, T., Harger, A., Niso-Santano, M., Zamzami, N., Scoazec, M., Durand, S., Enot, D. P., Fernández, Á. F., Martins, I., Kepp, O., Senovilla, L., Bauvy, C., … Kroemer, G. (2014). Regulation of Autophagy by Cytosolic Acetyl-Coenzyme A. *Molecular Cell*, *53*(5), 710–725. https://doi.org/10.1016/j.molcel.2014.01.016

Mariño, G., Pietrocola, F., Madeo, F., & Kroemer, G. (2014). Caloric restriction mimetics: Natural/physiological pharmacological autophagy inducers. *Autophagy*, *10*(11), 1879–1882. https://doi.org/10.4161/auto.36413

Mattson, M. P., Moehl, K., Ghena, N., Schmaedick, M., & Cheng, A. (2018). Intermittent metabolic switching, neuroplasticity and brain health. *Nature Reviews Neuroscience*, *19*(2), 81–94. https://doi.org/10.1038/nrn.2017.156

Mayer, C., Zhao, J., Yuan, X., & Grummt, I. (2004). mTOR-dependent activation of the transcription factor TIF-IA links rRNA synthesis to nutrient availability. *Genes & Development*, *18*(4), 423–434. https://doi.org/10.1101/gad.285504

McGrath, K. H., Haller, W., & Bines, J. E. (2023). Starvation and fasting: Biochemical aspects. In *Encyclopedia of Human Nutrition* (pp. 645–656). Elsevier. https://doi.org/10.1016/B978-0-12-821848-8.00068-8

McGuinness, O. P. (2026). Overview of Metabolism & the Provision of Metabolic Fuels. In P. J. Kennelly, K. M. Botham, O. P. McGuinness, & P. A. Weil (Eds.), *Harper's Illustrated Biochemistry, 33rd Edition* (Book, Section). McGraw Hill. accessmedicine.mhmedical.com/content.aspx?aid=1221937630

Melnikov, S., Mailliot, J., Shin, B.-S., Rigger, L., Yusupova, G., Micura, R., Dever, T. E., & Yusupov, M. (2016). Crystal Structure of Hypusine-Containing Translation Factor eIF5A Bound to a Rotated Eukaryotic Ribosome. *Journal of Molecular Biology*, *428*(18), 3570–3576. https://doi.org/10.1016/j.jmb.2016.05.011

Metur, S. P. (2024). *Understanding the Role of RNA-binding Proteins in Regulating Autophagy During Nutrient Limitation* [Dissertation, University of Michigan]. https://doi.org/10.7302/24071

Metur, S. P., & Klionsky, D. J. (2024). Nutrient□dependent signaling pathways that control autophagy in yeast. *FEBS Letters*, *598*(1), 32–47. https://doi.org/10.1002/1873-3468.14741

Michiels, C. F., Kurdi, A., Timmermans, J.-P., De Meyer, G. R. Y., & Martinet, W. (2016). Spermidine reduces lipid accumulation and necrotic core formation in atherosclerotic plaques via induction of autophagy. *Atherosclerosis*, *251*, 319–327. https://doi.org/10.1016/j.atherosclerosis.2016.07.899

Minois, N., Carmona-Gutierrez, D., Bauer, M. A., Rockenfeller, P., Eisenberg, T., Brandhorst, S., Sigrist, S. J., Kroemer, G., & Madeo, F. (2012). Spermidine promotes stress resistance in Drosophila melanogaster through autophagy-dependent and -independent pathways. *Cell Death & Disease*, *3*(10), e401–e401. https://doi.org/10.1038/cddis.2012.139

Mizushima, N. (2010). The role of the Atg1/ULK1 complex in autophagy regulation. *Current Opinion in Cell Biology*, *22*(2), 132–139. https://doi.org/10.1016/j.ceb.2009.12.004

Moinard, C., Cynober, L., & Debandt, J. (2005). Polyamines: Metabolism and implications in human diseases. *Clinical Nutrition*, *24*(2), 184–197. https://doi.org/10.1016/j.clnu.2004.11.001

Montalbano, S., Raboni, S., Sidoli, S., Mozzarelli, A., Bettati, S., & Buschini, A. (2023). Post-Translational Modifications of Histone Variants in the Absence and Presence of a Methionine-Depleting Enzyme in Normal and Cancer Cells. *Cancers*, *15*(2), 527. https://doi.org/10.3390/cancers15020527

Morris, S. M. (2007). Arginine Metabolism: Boundaries of Our Knowledge. *The Journal of Nutrition*, *137*(6), 1602S-1609S. https://doi.org/10.1093/jn/137.6.1602S

Morris, S. M. (2016). Arginine Metabolism Revisited. *The Journal of Nutrition*, *146*(12), 2579S-2586S. https://doi.org/10.3945/jn.115.226621

Most, J., Tosti, V., Redman, L. M., & Fontana, L. (2017). Calorie restriction in humans: An update. *Ageing Research Reviews*, *39*, 36–45. https://doi.org/10.1016/j.arr.2016.08.005

Mund, C., Sinha, A., Aderhold, A., Mateska, I., Hagag, E., Traikov, S., Gercken, B., Soto, A., Pollock, J., Arndt, L., Wölk, M., Werner, N., Fodelianaki, G., Subramanian, P., Chung, K.-J., Grossklaus, S., Langner, M., Elgendy, M., Grinenko, T., … Alexaki, V. I. (2025). A key role of polyamine metabolism in adipose tissue homeostasis that regulates obesity. *Metabolism*, *172*, 156358. https://doi.org/10.1016/j.metabol.2025.156358

Munro, H. N., Hubert, C., & Baliga, B. S. (1975). Regulation of Protein Synthesis in Relation to Amino Acid Supply—A Review**Unpublished experiments reported here by us were supported by the U.S. Public Health Service grants CA 08893–05 and AM 15364–02. In *Alcohol and Abnormal Protein Biosynthesis* (pp. 33–66). Elsevier. https://doi.org/10.1016/B978-0-08-017708-3.50010-0

Naito, T., Kuma, A., & Mizushima, N. (2013). Differential Contribution of Insulin and Amino Acids to the mTORC1-Autophagy Pathway in the Liver and Muscle. *Journal of Biological Chemistry*, *288*(29), 21074–21081. https://doi.org/10.1074/jbc.M113.456228

Nakanishi, S., & Cleveland, J. L. (2021). Polyamine Homeostasis in Development and Disease. *Medical Sciences*, *9*(2), 28. https://doi.org/10.3390/medsci9020028

Neinast, M., Murashige, D., & Arany, Z. (2019). Branched Chain Amino Acids. *Annual Review of Physiology*, *81*(1), 139–164. https://doi.org/10.1146/annurev-physiol-020518-114455

Nelson, D. L., Cox, M. M., Hoskins, A. A., & Lehninger, A. L. (2021). *Lehninger principles of biochemistry* (Eighth edition). Macmillan International Higher Education.

Neves, D., Martins, M. J., Dos Passos, E., & Tomada, I. (2015). To eat or not to eat – Anti□ageing effects of energy restriction. In D. Neves (Ed.), *Anti□ageing nutrients* (1st ed., pp. 33–132). Wiley. https://doi.org/10.1002/9781118823408.ch2

Noda, N. N., Ohsumi, Y., & Inagaki, F. (2009). ATG Systems from the Protein Structural Point of View. *Chemical Reviews*, *109*(4), 1587–1598. https://doi.org/10.1021/cr800459r

Nsi-Emvo, E., Chaton, B., Foltzer-Jourdainne, C., Gosse, F., & Raul, F. (1996). Premature expression of sucrase-isomaltase triggered by corticoid-dependent changes in polyamine metabolism. *American Journal of Physiology-Gastrointestinal and Liver Physiology*, *270*(1), G54–G59. https://doi.org/10.1152/ajpgi.1996.270.1.G54

Ocaña-Wilhelmi, L., Cardona, F., Garrido-Sanchez, L., Fernandez-Garcia, D., Tinahones, F. J., & Ramos-Molina, B. (2020). Change in serum polyamine metabolome pattern after bariatric surgery in obese patients with metabolic syndrome. *Surgery for Obesity and Related Diseases*, *16*(2), 306–311. https://doi.org/10.1016/j.soard.2019.10.024

Okabe, K. (1993). Assessment of Emaciation in Relation to Threat to Life in Anorexia Nervosa. *Internal Medicine*, *32*(11), 837–842. https://doi.org/10.2169/internalmedicine.32.837

Ouyang, Y., Wu, Q., Li, J., Sun, S., & Sun, S. (2020). S□adenosylmethionine: A metabolite critical to the regulation of autophagy. *Cell Proliferation*, *53*(11), e12891. https://doi.org/10.1111/cpr.12891

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., … Moher, D. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ*, n71. https://doi.org/10.1136/bmj.n71

Park, M. H., & Wolff, E. C. (2018). Hypusine, a polyamine-derived amino acid critical for eukaryotic translation. *Journal of Biological Chemistry*, *293*(48), 18710–18718. https://doi.org/10.1074/jbc.TM118.003341

Parkhitko, A. A., Filine, E., Mohr, S. E., Moskalev, A., & Perrimon, N. (2020). Targeting metabolic pathways for extension of lifespan and healthspan across multiple species. *Ageing Research Reviews*, *64*, 101188. https://doi.org/10.1016/j.arr.2020.101188

Pavlov, M. Y., Watts, R. E., Tan, Z., Cornish, V. W., Ehrenberg, M., & Forster, A. C. (2009). Slow peptide bond formation by proline and other *N* -alkylamino acids in translation. *Proceedings of the National Academy of Sciences*, *106*(1), 50–54. https://doi.org/10.1073/pnas.0809211106

Pegg, A. E. (2009). Mammalian polyamine metabolism and function. *IUBMB Life*, *61*(9), 880–894. https://doi.org/10.1002/iub.230

Peters, M. D. J., Godfrey, C. M., Khalil, H., McInerney, P., Parker, D., & Soares, C. B. (2015). Guidance for conducting systematic scoping reviews. *International Journal of Evidence-Based Healthcare*, *13*(3), 141–146. https://doi.org/10.1097/XEB.0000000000000050

Pietrocola, F., Lachkar, S., Enot, D. P., Niso-Santano, M., Bravo-San Pedro, J. M., Sica, V., Izzo, V., Maiuri, M. C., Madeo, F., Mariño, G., & Kroemer, G. (2015). Spermidine induces autophagy by inhibiting the acetyltransferase EP300. *Cell Death & Differentiation*, *22*(3), 509–516. https://doi.org/10.1038/cdd.2014.215

Pinkerton, M., & Barrientos, A. (2023). Diet restriction-induced mitochondrial signaling and healthy aging. In *Molecular Nutrition and Mitochondria* (pp. 587–632). Elsevier. https://doi.org/10.1016/B978-0-323-90256-4.00027-8

Pires, S. A. P., Soares, J. C., Luz, A. M. B. D., & Moleiro, P. (2020). OUTPATIENT ANALYTIC ASSESSMENT OF ANOREXIA NERVOSA — THE IMPORTANCE OF VENOUS BLOOD GASES. *Revista Paulista de Pediatria*, *38*, e2018358. https://doi.org/10.1590/1984-0462/2020/38/2018358

Proietti, E., Rossini, S., Grohmann, U., & Mondanelli, G. (2020). Polyamines and Kynurenines at the Intersection of Immune Modulation. *Trends in Immunology*, *41*(11), 1037–1050. https://doi.org/10.1016/j.it.2020.09.007

Puleston, D. J., Villa, M., & Pearce, E. L. (2017). Ancillary Activity: Beyond Core Metabolism in Immune Cells. *Cell Metabolism*, *26*(1), 131–141. https://doi.org/10.1016/j.cmet.2017.06.019

Puleston, D. J., Zhang, H., Powell, T. J., Lipina, E., Sims, S., Panse, I., Watson, A. S., Cerundolo, V., Townsend, A. R., Klenerman, P., & Simon, A. K. (2014). Autophagy is a critical regulator of memory CD8+ T cell formation. *eLife*, *3*, e03706. https://doi.org/10.7554/eLife.03706

Ramos-Molina, B., Lambertos, A., Lopez-Contreras, A. J., Kasprzak, J. M., Czerwoniec, A., Bujnicki, J. M., Cremades, A., & Peñafiel, R. (2014). Structural and degradative aspects of ornithine decarboxylase antizyme inhibitor 2. *FEBS Open Bio*, *4*(1), 510–521. https://doi.org/10.1016/j.fob.2014.05.004

Ramos-Molina, B., Queipo-Ortuño, M. I., Lambertos, A., Tinahones, F. J., & Peñafiel, R. (2019). Dietary and Gut Microbiota Polyamines in Obesity- and Age-Related Diseases. *Frontiers in Nutrition*, *6*, 24. https://doi.org/10.3389/fnut.2019.00024

Ray, R. M., Bavaria, M., & Johnson, L. R. (2015). Interaction of polyamines and mTOR signaling in the synthesis of antizyme (AZ). *Cellular Signalling*, *27*(9), 1850–1859. https://doi.org/10.1016/j.cellsig.2015.06.002

Ray, R. M., Bhattacharya, S., Bavaria, M. N., Viar, M. J., & Johnson, L. R. (2014). Spermidine, a sensor for antizyme 1 expression regulates intracellular polyamine homeostasis. *Amino Acids*, *46*(8), 2005–2013. https://doi.org/10.1007/s00726-014-1757-4

Ray, R. M., Viar, M. J., & Johnson, L. R. (2012). Amino Acids Regulate Expression of Antizyme-1 to Modulate Ornithine Decarboxylase Activity. *Journal of Biological Chemistry*, *287*(6), 3674–3690. https://doi.org/10.1074/jbc.M111.232561

Rehman, S. U., Ali, R., Zhang, H., Zafar, M. H., & Wang, M. (2023). Research progress in the role and mechanism of Leucine in regulating animal growth and development. *Frontiers in Physiology*, *14*, 1252089. https://doi.org/10.3389/fphys.2023.1252089

Rousseau, D., Kaspar, R., Rosenwald, I., Gehrke, L., & Sonenberg, N. (1996). Translation initiation of ornithine decarboxylase and nucleocytoplasmic transport of cyclin D1 mRNA are increased in cells overexpressing eukaryotic initiation factor 4E. *Proceedings of the National Academy of Sciences*, *93*(3), 1065–1070. https://doi.org/10.1073/pnas.93.3.1065

Ruan, H.-B., Ma, Y., Torres, S., Zhang, B., Feriod, C., Heck, R. M., Qian, K., Fu, M., Li, X., Nathanson, M. H., Bennett, A. M., Nie, Y., Ehrlich, B. E., & Yang, X. (2017). Calcium-dependent O-GlcNAc signaling drives liver autophagy in adaptation to starvation. *Genes & Development*, *31*(16), 1655–1665. https://doi.org/10.1101/gad.305441.117

Rubinsztein, D. C., Codogno, P., & Levine, B. (2012). Autophagy modulation as a potential therapeutic target for diverse diseases. *Nature Reviews Drug Discovery*, *11*(9), 709–730. https://doi.org/10.1038/nrd3802

Russell, R. C., Yuan, H.-X., & Guan, K.-L. (2014). Autophagy regulation by nutrient signaling. *Cell Research*, *24*(1), 42–57. https://doi.org/10.1038/cr.2013.166

Sabatini, D. M. (2017). Twenty-five years of mTOR: Uncovering the link from nutrients to growth. *Proceedings of the National Academy of Sciences*, *114*(45), 11818–11825. https://doi.org/10.1073/pnas.1716173114

Sagar, N. A., Tarafdar, S., Agarwal, S., Tarafdar, A., & Sharma, S. (2021). Polyamines: Functions, Metabolism, and Role in Human Disease Management. *Medical Sciences*, *9*(2), 44. https://doi.org/10.3390/medsci9020044

Sailer, M. (2012). *Metabolic interrelationships of amino acid metabolism in health and disease.* [Dissertation, TUM School of Life Sciences Technical University of Munich, Germany.]. chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://mediatum.ub.tum.de/doc/1118393/1118393.pdf

Saxton, R. A., & Sabatini, D. M. (2017). mTOR Signaling in Growth, Metabolism, and Disease. *Cell*, *168*(6), 960–976. https://doi.org/10.1016/j.cell.2017.02.004

Schertel, B., & Eichler, W. (1991). Polyamine Biosynthesis in Arginine-Starved and Refed Rats. *Biological Chemistry Hoppe-Seyler*, *372*(1), 27–34. https://doi.org/10.1515/bchm3.1991.372.1.27

Schmidt, C., Becker, T., Heuer, A., Braunger, K., Shanmuganathan, V., Pech, M., Berninghausen, O., Wilson, D. N., & Beckmann, R. (2016). Structure of the hypusinylated eukaryotic translation factor eIF-5A bound to the ribosome. *Nucleic Acids Research*, *44*(4), 1944–1951. https://doi.org/10.1093/nar/gkv1517

Schroeder, S., Pendl, T., Zimmermann, A., Eisenberg, T., Carmona-Gutierrez, D., Ruckenstuhl, C., Mariño, G., Pietrocola, F., Harger, A., Magnes, C., Sinner, F., Pieber, T. R., Dengjel, J., Sigrist, S. J., Kroemer, G., &

Madeo, F. (2014). Acetyl-coenzyme A: A metabolic master regulator of autophagy and longevity. *Autophagy*, *10*(7), 1335–1337. https://doi.org/10.4161/auto.28919

Schuller, A. P., Wu, C. C.-C., Dever, T. E., Buskirk, A. R., & Green, R. (2017). eIF5A Functions Globally in Translation Elongation and Termination. *Molecular Cell*, *66*(2), 194-205.e5. https://doi.org/10.1016/j.molcel.2017.03.003

Seale, B., Slotabec, L., Nguyen, J. D., Wang, H., Patterson, C., Filho, F., Rouhi, N., Adenawoola, M. I., & Li, J. (2024). Sestrin2 serves as a scaffold protein to maintain cardiac energy and metabolic homeostasis during pathological stress. *The FASEB Journal*, *38*(20), e70106. https://doi.org/10.1096/fj.202401404R

Seiler, N., Bolkenius, F. N., & Sarhan, S. (1981). Formation of acetylpolyamines in the liver of fasting animals. *International Journal of Biochemistry*, *13*(12), 1205–1214. https://doi.org/10.1016/0020-711X(81)90066-5

Settembre, C., Zoncu, R., Medina, D. L., Vetrini, F., Erdin, S., Erdin, S., Huynh, T., Ferron, M., Karsenty, G., Vellard, M. C., Facchinetti, V., Sabatini, D. M., & Ballabio, A. (2012). A lysosome-to-nucleus signalling mechanism senses and regulates the lysosome via mTOR and TFEB: Self-regulation of the lysosome via mTOR and TFEB. *The EMBO Journal*, *31*(5), 1095–1108. https://doi.org/10.1038/emboj.2012.32

Shen, Y., & Czaja, M. J. (2019). A Novel Mechanism of Starvation□Stimulated Hepatic Autophagy: Calcium□Induced O□GlcNAc□Dependent Signaling. *Hepatology*, *69*(1), 446–448. https://doi.org/10.1002/hep.30118

Sivashanmugam, M., J., J., V., U., & K.N., S. (2017). Ornithine and its role in metabolic diseases: An appraisal. *Biomedicine & Pharmacotherapy*, *86*, 185–194. https://doi.org/10.1016/j.biopha.2016.12.024

Stegehake, D., Kurosinski, M.-A., Schürmann, S., Daniel, J., Lüersen, K., & Liebau, E. (2015). Polyamine-independent Expression of Caenorhabditis elegans Antizyme. *Journal of Biological Chemistry*, *290*(29), 18090–18101. https://doi.org/10.1074/jbc.M115.644385

Stheneur, C., Blanchet, C., Mattar, L., Dicembre, M., Wilson, K., EVHAN Group, Duclos, J., Roux, H., Thiébaud, M.-R., Vibert, S., Hubert, T., Courty, A., Ringuenet, D., Benoit, J.-P., Moro, M.-R., Bignami, L., Nordon, C., Rouillon, F., Cook, S., … Godart, N. (2024). Determinants and risk factors for renal damage: Where do patients hospitalized for severe anorexia nervosa stand? A multi-center study. *Journal of Eating Disorders*, *12*(1), 72. https://doi.org/10.1186/s40337-024-01024-w

Strøm, A., Jensen, R. A., Oslo, M. D., & Oslo, M. D. (1951). MORTALITY FROM CIRCULATORY DISEASES IN NORWAY 1940-1945. *The Lancet*, *257*(6647), 126–129. https://doi.org/10.1016/S0140-6736(51)91210-X

Szaflarski, W., Leśniczak-Staszak, M., Sowiński, M., Ojha, S., Aulas, A., Dave, D., Malla, S., Anderson, P., Ivanov, P., & Lyons, S. M. (2022). Early rRNA processing is a stress-dependent regulatory event whose inhibition maintains nucleolar integrity. *Nucleic Acids Research*, *50*(2), 1033–1051. https://doi.org/10.1093/nar/gkab1231

Takahara, T., Amemiya, Y., Sugiyama, R., Maki, M., & Shibata, H. (2020). Amino acid-dependent control of mTORC1 signaling: A variety of regulatory modes. *Journal of Biomedical Science*, *27*(1), 87. https://doi.org/10.1186/s12929-020-00679-2

Tomita, K., Haga, H., Ishii, G., Katsumi, T., Sato, C., Aso, R., Okumoto, K., Nishise, Y., Watanabe, H., Saito, T., Otani, K., & Ueno, Y. (2014). Clinical manifestations of liver injury in patients with anorexia nervosa. *Hepatology Research*, *44*(10). https://doi.org/10.1111/hepr.12202

Torres, N., Tobón-Cornejo, S., Velazquez-Villegas, L. A., Noriega, L. G., Alemán-Escondrillas, G., & Tovar, A. R. (2023). Amino Acid Catabolism: An Overlooked Area of Metabolism. *Nutrients*, *15*(15), 3378. https://doi.org/10.3390/nu15153378

Tseng, Y.-J. (2023). *Repeat-associated non-AUG (RAN) Translation in GC-Rich Repeats of C9ALS/FTD and FXTAS* [Dissertation, University of Michigan]. https://doi.org/10.7302/8546

Urschel, K. L. (2007). *Arginine synthesis and metabolism in neonatal piglets* [Dissertation, University of Alberta Library]. https://doi.org/10.7939/R3-V9M0-5D77

Vernieri, C., Casola, S., Foiani, M., Pietrantonio, F., De Braud, F., & Longo, V. (2016). Targeting Cancer Metabolism: Dietary and Pharmacologic Interventions. *Cancer Discovery*, *6*(12), 1315–1333. https://doi.org/10.1158/2159-8290.CD-16-0615

Viola, A., & Bronte, V. (2007). Metabolic mechanisms of cancer-induced inhibition of immune responses. *Seminars in Cancer Biology*, *17*(4), 309–316. https://doi.org/10.1016/j.semcancer.2007.06.005

Wang, H., Huang, B., Wang, W., Li, J., Chen, Y., Flynn, T., Zhao, M., Zhou, Z., Lin, X., Zhang, Y., Xu, M., Li, K., Tian, K., Yuan, D., Zhou, P., Hu, L., Zhong, D., Zhu, S., Li, J., … Yang, B. (2019). High urea induces

depression and LTP impairment through mTOR signalling suppression caused by carbamylation. *EBioMedicine*, *48*, 478–490. https://doi.org/10.1016/j.ebiom.2019.09.049

Wang, Y.-P., & Lei, Q.-Y. (2018). Metabolite sensing and signaling in cell metabolism. *Signal Transduction and Targeted Therapy*, *3*(1), 30. https://doi.org/10.1038/s41392-018-0024-7

Wątor, E., Wilk, P., Biela, A., Rawski, M., Zak, K. M., Steinchen, W., Bange, G., Glatt, S., & Grudnik, P. (2023). Cryo-EM structure of human eIF5A-DHS complex reveals the molecular basis of hypusination-associated neurodegenerative disorders. *Nature Communications*, *14*(1), 1698. https://doi.org/10.1038/s41467-023-37305-2

Weber, G., Ferdinandus, J. A., Queener, S. F., Dunaway, G. A., & Trailan, L. J.-P. (1972). Metabolic Imbalance in Carbohydrate, Pyrimidine and Ornithine Utilization. *Advances in Enzyme Regulation*, *10*, 39–62. https://doi.org/10.1016/0065-2571(72)90005-2

Wei, L. H., Wu, G., Morris, S. M., & Ignarro, L. J. (2001). Elevated arginase I expression in rat aortic smooth muscle cells increases cell proliferation. *Proceedings of the National Academy of Sciences*, *98*(16), 9260–9264. https://doi.org/10.1073/pnas.161294898

Wei, Z., Liu, X., Cheng, C., Yu, W., & Yi, P. (2021). Metabolism of Amino Acids in Cancer. *Frontiers in Cell and Developmental Biology*, *8*, 603837. https://doi.org/10.3389/fcell.2020.603837

Wesselborg, S., & Stork, B. (2015). Autophagy signal transduction by ATG proteins: From hierarchies to networks. *Cellular and Molecular Life Sciences*, *72*(24), 4721–4757. https://doi.org/10.1007/s00018-015-2034-8

Willcox, B. J., Willcox, D. C., Todoriki, H., Fujiyoshi, A., Yano, K., He, Q., Curb, J. D., & Suzuki, M. (2007). Caloric Restriction, the Traditional Okinawan Diet, and Healthy Aging: The Diet of the World's Longest□Lived People and Its Potential Impact on Morbidity and Life Span. *Annals of the New York Academy of Sciences*, *1114*(1), 434–455. https://doi.org/10.1196/annals.1396.037

Wolfson, R. L., Chantranupong, L., Saxton, R. A., Shen, K., Scaria, S. M., Cantor, J. R., & Sabatini, D. M. (2016). Sestrin2 is a leucine sensor for the mTORC1 pathway. *Science*, *351*(6268), 43–48. https://doi.org/10.1126/science.aab2674

Wu, G., & Morris, S. M. (1998). Arginine metabolism: Nitric oxide and beyond. *Biochemical Journal*, *336*(1), 1–17. https://doi.org/10.1042/bj3360001

Wu, R. (2020). *Polyamines metabolism in T lymphocytes.* [Dissertation, Graduate School at The Ohio State University.]. http://rave.ohiolink.edu/etdc/view?acc_num=osu1610025430849083

Wu, X., Xie, W., Xie, W., Wei, W., & Guo, J. (2022). Beyond controlling cell size: Functional analyses of S6K in tumorigenesis. *Cell Death & Disease*, *13*(7), 646. https://doi.org/10.1038/s41419-022-05081-4

Wu, Z., Hu, C.-A. A., Wu, G., Zhaorigetu, S., Chand, H., Sun, K., Ji, Y., Wang, B., Dai, Z., Walton, B., Miao, Y., & Hou, Y. (2015). Intimacy and a deadly feud: The interplay of autophagy and apoptosis mediated by amino acids. *Amino Acids*, *47*(10), 2089–2099. https://doi.org/10.1007/s00726-015-2084-0

Yang, H., Wiré, M., Permert, J., Söderholm, J., Braaf, Y., & Larsson, J. (1999). Early response of ornithine decarboxylase activity and energy metabolism to postsurgery refeeding in rat small intestine. *Clinical Nutrition*, *18*(1), 41–45. https://doi.org/10.1016/S0261-5614(99)80048-X

Yu, C.-H., Chou, C.-C., Lee, Y.-J., Khoo, K.-H., & Chang, G.-D. (2015). Uncovering protein polyamination by the spermine-specific antiserum and mass spectrometric analysis. *Amino Acids*, *47*(3), 469–481. https://doi.org/10.1007/s00726-014-1879-8

Zahedi, K., Barone, S., & Soleimani, M. (2022). Polyamines and Their Metabolism: From the Maintenance of Physiological Homeostasis to the Mediation of Disease. *Medical Sciences*, *10*(3), 38. https://doi.org/10.3390/medsci10030038

Zhang, C., Zhen, Y., Weng, Y., Lin, J., Xu, X., Ma, J., Zhong, Y., & Wang, M. (2025). Research progress on the microbial metabolism and transport of polyamines and their roles in animal gut homeostasis. *Journal of Animal Science and Biotechnology*, *16*(1), 57. https://doi.org/10.1186/s40104-025-01193-x

Zhang, H., Alsaleh, G., Feltham, J., Sun, Y., Napolitano, G., Riffelmacher, T., Charles, P., Frau, L., Hublitz, P., Yu, Z., Mohammed, S., Ballabio, A., Balabanov, S., Mellor, J., & Simon, A. K. (2019). Polyamines Control eIF5A Hypusination, TFEB Translation, and Autophagy to Reverse B Cell Senescence. *Molecular Cell*, *76*(1), 110-125.e9. https://doi.org/10.1016/j.molcel.2019.08.005

Zhou, D. R., Eid, R., Miller, K. A., Boucher, E., Mandato, C. A., & Greenwood, M. T. (2019). Intracellular second messengers mediate stress inducible hormesis and Programmed Cell Death: A review. *Biochimica et Biophysica Acta (BBA) - Molecular Cell Research*, *1866*(5), 773–792. https://doi.org/10.1016/j.bbamcr.2019.01.016

Zwighaft, Z., Aviram, R., Shalev, M., Rousso-Noori, L., Kraut-Cohen, J., Golik, M., Brandis, A., Reinke, H., Aharoni, A., Kahana, C., & Asher, G. (2015). Circadian Clock Control by Polyamine Levels through a Mechanism that Declines with Age. *Cell Metabolism*, *22*(5), 874–885. https://doi.org/10.1016/j.cmet.2015.09.011