Medical Science

To Cite:
Zgrzywa Z, Tucka B, Szyszkowski J, Zawadzka I, Wądołowska P, Kowalski B, Kriese N, Komorowska E, Jaworski J, Kucharski T. Impact of diet and lifestyle interventions on core molecular longevity pathways and the human healthspan: a mechanistic review. *Medical Science* 2026; 30: e56ms3805
doi: https://doi.org/10.54905/disssi.v30i169.e56ms3805

Authors' Affiliation:
Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland

***Corresponding author:**
Zuzanna Zgrzywa,
Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland,
Email: zuziazgrzywa@wp.pl; ph; +48 725978502

ORCID

Zuzanna Zgrzywa	0009-0005-1032-8063
Brygida Tucka	0009-0004-1785-2186
Jakub Szyszkowski	0009-0000-3217-6981
Izabella Zawadzka	0009-0008-3149-2550
Paulina Wądołowska	0009-0005-5646-1775
Bartłomiej Kowalski	0009-0003-5856-2663
Natalia Kriese	0009-0001-8278-1044
Ewelina Komorowska	0009-0001-4103-7745
Jakub Jaworski	0009-0004-7140-9679
Tomasz Kucharski	0009-0007-5647-9021

Peer-Review History
Received: 21 August 2025
Reviewed & Revised: 07/September/2025 to 23/February/2026
Accepted: 03 March 2026
Published: 16 March 2026

Peer-review Method
External peer-review was done through double-blind method.

Medical Science
pISSN 2321–7359; eISSN 2321–7367

DISCOVERY SCIENTIFIC SOCIETY

Impact of diet and lifestyle interventions on core molecular longevity pathways and the human healthspan: a mechanistic review

Zuzanna Zgrzywa*, Brygida Tucka, Jakub Szyszkowski, Izabella Zawadzka, Paulina Wądołowska, Bartłomiej Kowalski, Natalia Kriese, Ewelina Komorowska, Jakub Jaworski, Tomasz Kucharski

ABSTRACT

Aging is a complex, multifactorial biological process and the primary risk factor for chronic disease. While genetic factors play a role, environmental interventions—specifically diet and lifestyle—profoundly impact the rate and quality of human aging. This mechanistic narrative review integrates recent advances, focusing on the dynamic modulation and synergistic interactions between interventions and core longevity pathways. We examine how caloric restriction (CR), intermittent fasting (IF), and macronutrient ratios—especially protein restriction (PR)—affect key molecular pathways, including the sirtuin, AMP-activated protein kinase (AMPK), and Mechanistic Target of Rapamycin (mTOR) pathways. We also show how this work relates to human clinical work and how it affects new biomarkers, such as the epigenetic clock, as well as the gut microbiome's impact on long-term diet-related outcomes. We also have an interactive model that illustrates how physical activity and diet interact along these pathways, highlighting mechanisms such as hormesis and interorgan communication. Understanding these linked processes will be essential to devising personalized longevity approaches to lengthen human healthspan and reverse age-related decline.

Keywords: Aging; Dietary Interventions; Longevity Pathways; Epigenetic Clock; mTOR

1. INTRODUCTION

The multifactorial nature of aging makes it a risk factor for various chronic diseases of the cardiovascular, nervous, and metabolic systems, as well as for cancer (López-Otín et al., 2023). As global life expectancy increases, there is a growing need to shift the focus of research from simply extending lifespan to enhancing healthspan—the period of life spent in good health and free of disease. Although genetics affects the rate of aging, a growing body of evidence indicates that environmental determinants, such as diet and lifestyle, heavily influence the aging process and are modifiable.

1.1. Hallmarks of Aging: Nutrient-Sensitive Pathways

A series of interrelated biological features characterizes the molecular basis of aging. Researchers described this concept a decade ago and have recently revised it to encompass an "expanding galaxy" of aging mechanisms (López-Otín et al., 2023). Cellular senescence is one of the mechanisms that contribute to tissue dysfunction (Campisi, 2013). Of the various hallmarks of aging, three are particularly sensitive to nutritional and environmental signals: Deregulated Nutrient Sensing, Mitochondrial Dysfunction, and Loss of Proteostasis. Together, they contribute to the gradual decline in cellular homeostasis (Kennedy and Lamming, 2016).

Among the core molecular pathways orchestrating these hallmarks are the Sirtuin family of deacetylases, the Mechanistic Target of Rapamycin (mTOR) signaling pathway, and the AMP-activated protein kinase (AMPK) signaling pathway. These are the genetically encoded mechanisms that evolution has conserved, and that evidence implicates in longevity (Kenyon, 2010). Affecting these pathways through nutrition or energy balance directly influences cellular repair, energy metabolism, and genomic stability.

An understanding of how specific interventions (e.g., caloric restriction (CR), intermittent fasting (IF), and complex dietary regimens) may affect these sensors is, therefore, critical for crafting anti-aging therapeutics.

1.2. Review objectives and strategy for literature selection

Although the basic functions of CR and IF in individual molecular pathways, such as mTOR inhibition, have now been reviewed in depth, an extensive integration of different interventions remains missing. It also does not adequately address their synergistic effects or validate outcomes using objective, translational biomarkers in human cohorts.

Therefore, the primary objective of this review is to analyze the molecular crosstalk between various dietary and lifestyle interventions and the core longevity pathways (mTOR, Sirtuins, AMPK). The goal is to develop an interactive model that shows how different interventions interact to maintain cellular balance. Alongside that, there is a need to take a close look at how these findings might translate to real-world use—especially when it comes to using new biomarkers, such as the epigenetic clock, and multi-omics data to assess how well these interventions perform in human aging. It is about figuring out how valuable these tools really are in tracking the effects, not just knowing they exist.

This article has been written as a mechanistic narrative review, using a structured, targeted search of the literature to identify recent conceptually relevant studies rather than to capture all available documents. We conducted a systematic search of the primary literature in Scopus, PubMed/MEDLINE, and Web of Science, considering a five-year time window (2020–2025) to cover recent developments, and we included seminal classical papers (pre-2020) considered as the definition of the core molecular pathways. Search terms were linked together with Boolean operators and sorted into four main categories: Core Aging and Longevity (aging OR senescence OR longevity OR "healthspan"); Dietary and Lifestyle Interventions: ("caloric restriction" OR "intermittent fasting" OR "Mediterranean diet" OR "dietary intervention" OR "exercise" OR "sleep"); Molecular Pathways: (mTOR OR Sirtuins OR AMPK OR "autophagy" OR "IGF-1 (Insulin-like growth factor 1)" OR "nutrient sensing"); Innovative/Translational Aspects: ("epigenetic clock" OR "biomarkers of aging" OR "omics" OR "translational science" OR "gut microbiome") Example Search String (for PubMed): ((aging AND mTOR) OR (longevity AND sirtuin)) AND ("caloric restriction" OR "intermittent fasting" OR exercise) AND (human OR clinical OR translational) AND (2020:2025[dp]).

The criteria for inclusion in this review were English-language articles and reviews. We focused our review on work carried out in humans and primates, or on translatable in vivo and in vitro model systems, that directly probe the molecular networks modulated by diet, lifestyle, and longevity pathways. We included only articles on epigenetics, biomarkers, or multi-omics data associated with these interventions. Exclusion criteria consisted of the grey literature, such as conference abstracts and dissertations. We also removed any interventions that were not related to diet/lifestyle or did not explore molecular pathways associated with longevity; thus, we included only studies that had both epidemiological and mechanistic correlations. We also removed all articles published prior to 2020 from this review; however, we included seminal articles necessary to provide a foundation for this field of research, thereby achieving our objective of creating a comprehensive mechanistic framework. Finally, we did not attempt a quantitative synthesis of the published literature.

1.3. Structure of the Review

This review first outlines the Core Molecular Pathways and then conducts a comprehensive review of Dietary Strategies and Mechanistic Crosstalk. The work culminates in a discussion of Integration and Synergy and the crucial Translational Impact and Novel Biomarkers of Aging, culminating in concluding remarks on future research directions.

2. CORE MOLECULAR PATHWAYS OF LONGEVITY

A complex interplay of molecular mechanisms, including telomere attrition and genomic instability (Shammas, 2011), drives the aging process, and researchers recognize three of these mechanisms as critically sensitive to nutrient availability and energy status: the mTOR pathway, the Sirtuins, and the AMPK-Autophagy axis. These pathways function as cellular nutrient sensors, coordinating cell growth, maintenance, and survival in response to environmental cues (Longo and Panda, 2016). Notably, the predominant molecular pathways that mediate these hallmarks (such as mTOR, Sirtuins, and AMPK) are under substantial genetic regulation that shapes their baseline activity and their responses to signals from outside the cell (Kenyon, 2010).

2.1. The mTOR Pathway: A Key Regulator of Anabolism and Aging

The mTOR is a central controller of cell growth and cell cycle progression by sensing signals from nutrient and growth factor pathways (Zoncu et al., 2011). It predominantly promotes anabolism, including protein and lipid synthesis and cell growth, and represses catabolism, including autophagy. Chronic activation of the mTOR pathway—commonly caused by excess nutrient availability—is strongly associated with accelerated aging and aging-related diseases. Thus, inhibition of mTORC1 by either CR or drugs such as rapamycin is among the most potent means to increase longevity across diverse species.

2.2. Sirtuins: Protectors of Genomic Stability

Sirtuins are part of a nicotinamide adenine dinucleotide (NAD+)-dependent deacetylase family (SIRT1–SIRT7), which directly connects cellular energetics to gene expression and cell repair. Among them, Sirtuin 1 (SIRT1) is the best studied longevity factor. SIRT1 functions as a metabolic sensor, and a high NAD+/NADH ratio enhances its activity—a condition that usually arises during low energy intake or fasting (Cantó et al., 2015). The NAD+ dependence links cellular energy status directly to gene expression and cellular repair, acting as a conserved metabolic signal in the search for longevity (Guarente, 2015). SIRT1 is an important regulator of aging and a major determinant of longevity, deacetylating several critical substrate proteins. This enzymatic action leads to increased DNA repair to maintain genomic stability and to increased cellular energy homeostasis through enhanced mitochondrial biogenesis and function. Moreover, by modulating transcription factors such as NF-κB, SIRT1 effectively reduces chronic systemic inflammation, thereby counteracting the progressive decline known as inflammaging.

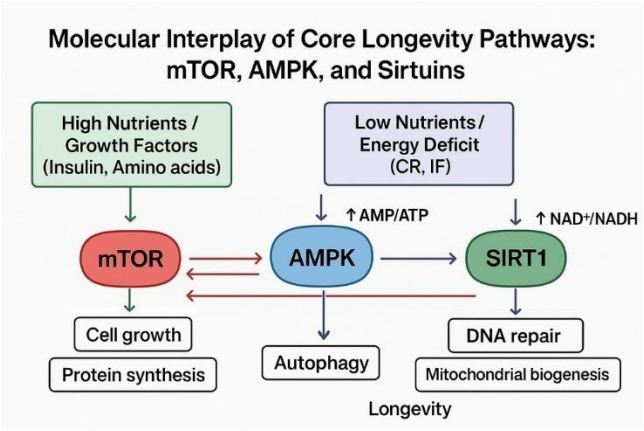

Figure 1. Schematic of cellular nutrient-sensing network. A nutrient-rich environment (amino acids, insulin/IGF-1) stimulates the mTOR pathway to enhance anabolism and growth, and suppresses AMPK and autophagy. In contrast, energy deficiency (fasting, caloric restriction) stimulates the fuel sensor AMPK and SIRT1 expression (as a consequence of increased NAD+ levels). This condition induces catabolism, DNA repair, and autophagy, which converge on cell maintenance and longevity. SIRT1 and AMPK reciprocally regulate each other (Adapted from: Longo and Brandhorst, 2020; Canto et al., 2012).

2.3. AMPK and Autophagy: Promoting Cellular Cleanup

The AMPK acts as a nutrient and energy sensor that regulates energy metabolism (Hardie et al., 2012). It is activated in response to compromised cellular energetics (energy consumption > energy supply, high AMP/ATP ratio) and is considered an energy-status sensor. Phosphorylated and activated AMPK promotes catabolic (energy-producing) pathways and inhibits anabolic (energy-consuming) pathways, and also acts as a functional antagonist of mTOR. This activation is also necessary to connect energy status to

Sirtuin activity, since AMPK modulates SIRT1 activity and oxidative metabolism. Important precursors, such as nicotinamide riboside, have been shown to stimulate oxidative metabolism, once again connecting diet to mitochondrial health (Cantó et al., 2012). The control of this essential turnover process is divided between nutrient sensing and energy demand, indicating pathways linking exercise to mitochondrial health (Vargas-Ortiz et al., 2019). In addition to mitochondrial function, AMPK is a master regulator of autophagy in skeletal muscle and is important for the removal of damaged organelles (He et al., 2012). AMPK activation is a potent trigger of autophagy—the vital cellular process that recycles and degrades damaged organelles and aggregated proteins (Mattson et al., 2017). Among them, a specialized form, mitophagy, selectively degrades damaged mitochondria. The AMPK-autophagy axis is also important in mitigating the accumulation of cellular damage that defines aging, by clearing cellular detritus and maintaining proteostasis. Figure 1 presents a summary of this key interaction.

3. DIETARY STRATEGIES AND MECHANISTIC CROSSTALK

Now that we have understood the main molecular targets, we can see how basic diets affect these pathways to increase longevity.

3.1. Caloric Restriction (CR) versus Intermittent Fasting (IF): A Molecular Comparison

Both CR—a chronic reduction in energy intake without undernutrition —and IF—which entails alternating periods of fasting and eating (with Time-Restricted Eating, TRE, as a variant) — are potent regulators of nutrient-sensing pathways. The CR model remains at the center of attention for its implications for healthy human aging (Anderson and Weindruch, 2012). The result of CR is sustained low-level signaling (Heilbronn and Ravussin, 2017), while IF takes advantage of oscillations between fed and fasted states to maximize protective effects and is emerging from animal and human studies as particularly beneficial for metabolic health (de Cabo and Mattson, 2019). The CR strategy involves a continuous reduction in IGF-1 signaling and a steady-state mild activation of AMPK, leading to increased NAD+ levels and, consequently, elevated SIRT1 activity (Guarente, 2015). CR promotes cellular homeostasis, in part, by indirectly enhancing the suppression of IGF-1 signaling and by activating AMPK to a moderate extent. The repertoire of signaling events altered by metabolism converges to provide persistent downregulation of mTORC1 activity, rendering the cell from growth and anabolism to repair and catabolism. On the other hand, the IF system produces a different type of pulsatile response. Extended fasting (batch) periods increase (upregulate) both autophagy and mitophagy, which are important for clearing damaged macromolecules (Mattson et al., 2017). Whereas CR uses long-term, low-level signals for control, IF uses the shift between fed and fasted states to quickly trigger protection mechanisms and create a direct relationship between circadian rhythms and metabolic health (Longo and Panda, 2016). There are some indications that TRE could have practical applications. Systematic reviews have substantiated its efficacy for weight reduction (Welton et al., 2020), and a 10-h protocol has enhanced blood pressure and atherogenic lipids (Wilkinson et al., 2020). It has also improved glycemic control (Cienfuegos et al., 2021).

3.2. Macrodietary Composition: Protein, Amino Acids, and Nutrient Sensing

Diet quality, especially macronutrient composition, affects cardiometabolic health and lifespan independently of energy quantity and often to a greater extent than energy intake (Solon-Biet et al., 2014). Concerning protein restriction (PR) and mTOR, dietary protein, and especially the concentration of essential amino acids, e.g., leucine and methionine, is a strong stimulator of mTORC1. This desire for fine-tuning is consistent with reports on protein quantity and source in fasting-mimicking diets (Brandhorst and Longo, 2019). Also, epidemiological evidence suggests that limiting protein intake results in a significant reduction in IGF-1, cancer, and all-cause mortality in individuals 65 years of age and younger (Levine et al., 2014). This finding suggests that PR represents a powerful, separate lever for modulating the aging process. Similarly, regarding lipids and inflammaging, the quality of dietary fats strongly influences chronic, low-grade inflammation. High consumption of omega-3 polyunsaturated fatty acids is associated with lower circulating levels of markers of systemic inflammation, mediated by resolvins that oppose NF-κB signaling. Therefore, this mechanism may have indirect anti-aging effects via the Sirtuin pathway, especially since dysfunctional communication between fat and muscle tissues is responsible for many age-related metabolic disorders (Fang et al., 2023).

3.3. Complex Dietary Patterns (e.g., Mediterranean Diet): Holistic Molecular Effects

The Mediterranean Diet (MedDiet) contains an abundance of vegetables, whole grains, and olive oil, and includes little red meat, and provides consistent evidence that it supports a higher healthspan (Mazza et al., 2021). Molecularly, the components of the MedDiet work synergistically to confer its beneficial properties. In terms of phytochemical composition and antioxidant properties, the high

levels of polyphenolic compounds (resveratrol, curcumin, etc.) found across all food groups comprising the MedDiet may serve as CR mimetics by directly activating or stabilizing SIRT1 and other stress response proteins (Timmers et al., 2011). Furthermore, regarding the gut microbiome as a mediator, the high fiber and polyphenol content promote a favorable gut microbiota composition and the resulting production of short-chain fatty acids (SCFAs), such as butyrate (Sanz et al., 2020). Since the gut microbiota changes significantly with age, its modulation is critical for maintaining health in older adults (O'Toole and Jeffery, 2015). Hence, the gut microbiota acts as a pivotal molecular mediator, converting dietary habits into longevity signals for the host.

4. INTEGRATION AND SYNERGY: BEYOND INDIVIDUAL INTERVENTIONS

The greatest promise for lifelong health and well-being lies not in the de novo generation of pairwise intervention cooperations but rather in elucidating the molecular modalities through which these interventions interact. The most significant potential to achieve this effect of sustainable human healthspan extension lies not in abandoning individual interventions but in understanding their molecular synergistic crosstalk. As a combined intervention may boost positive signals and activate different lifespan pathways, its effect may be greater than that of either diet or exercise alone.

4.1. Synergistic effects of diet and exercise on pathway regulation

Protection against age-related disease is an inherent by-product of telomere maintenance and senescence evasion. Exercise, particularly endurance training, induces a distinct but partially overlapping set of protective mechanisms, many of which converge with those influenced by dietary treatments. Regarding mitochondrial biogenesis, both CR—or fasting—and exercise are potent inducers of mitochondrial biogenesis and turnover. Exercise acts as a potent antioxidant by upregulating key enzymes involved in cellular adaptation, a process known as hormesis (Gomez-Cabrera et al., 2012). Compared with either treatment alone, this dual strategy potently upregulates master transcriptional regulators, such as peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α). Therefore, it stimulates mitochondrial biogenesis and reduces oxidative stress.

AMPK also regulates NAD+ metabolism; in addition, exercise rapidly activates AMPK in response to increased energy stress. CR further potentiates this activation by elevating the cellular AMP/ATP ratio. So, exercise and energy deficit synergistically influence the master kinase AMPK, a critical node that governs SIRT1 and oxidative metabolism (Cantó et al., 2012). Each intervention increases cellular NAD+ availability, and the significance of NAD+ precursors for mitochondrial function and metabolic health is rapidly emerging (van der Velpen et al., 2022). Finally, in the realm of epigenetic modulation, systems analysis of integrated responses to exercise training demonstrates coordinated metabolic and epigenetic responses across tissues (Zierer et al., 2015). In addition, researchers have recently proposed that exercise may have unique effects on the epigenome. Acute exercise rapidly remodels promoter methylation in human skeletal muscle genes (Barrès et al., 2012). This rapid remodeling highlights that changes in physical activity and other lifestyle factors influence epigenetic aging in skeletal muscle (Sillanpää et al., 2021).

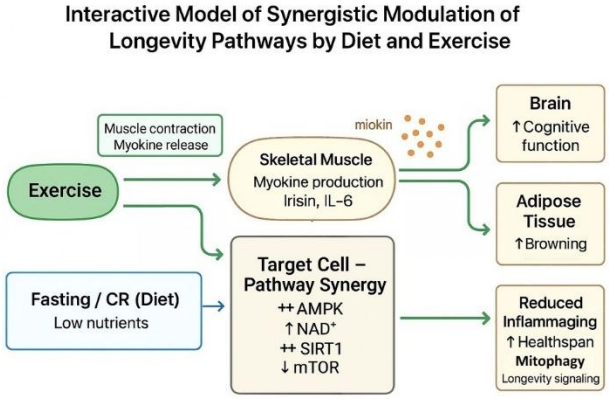

Figure 2. This model of inter-organ communication demonstrates the additive effects of the joint intervention. Dietary Interventions (e.g., IF/CR) induce a systemic low-nutrient/high-NAD+ milieu. Exercise-mediated muscle contraction results in the secretion of several myokines (e.g., irisin and IL-6). These myokines also have endocrine effects on distant organs (AT, Liver, Brain), potentiating the anti-aging signal (e.g., brown fat, AMPK, reduced inflammation) triggered by diet. The combined action amplifies mitochondrial biogenesis and longevity signals beyond the efficacy of a single intervention (Conceptual model based on findings from: Handschin and Spiegelman, 2020).

4.2. Molecular Crosstalk: The Interactive Model

To adequately capture the intricacies of this interaction, a dynamic model emphasizes the communication between organs. Exercise induces the release of myokines (hormone-like factors released by contracting muscle, including Irisin), making skeletal muscle a secretory organ (Pedersen and Febbraio, 2012). These contribute to significant crosstalk between organs (Safdar et al., 2016). Crosstalk between muscle, fat, and liver is especially important in the starved state. Myokine-mediated modulation of adipose-muscle communication may also enhance lipid utilization and insulin responsiveness (Fang et al., 2023), further boosting the CR-induced metabolic shift in distant tissues. The Interactive Model (Figure 2) illustrates this bilateral communication.

Concerning the elimination of senescent cells, dietary interventions (e.g., certain polyphenols) in conjunction with physical activity may work synergistically to remove senescent cells, which are a significant contributor to age-related dysfunction. Together, this dual targeting of the metabolic milieu and the clearance machinery could provide a superior strategy to diminish the cellular senescence load (Kirkland and Tchkonia, 2020).

5. IMPACT ON TRANSLATION AND NEW BIOMARKERS OF AGING

Although the translation of diet and lifestyle interventions from animal models into human clinical trials continues to be a considerable challenge, this section summarizes the current clinical evidence and suggests a small panel of objective biomarkers for the assessment of biological age and response to intervention (Kennedy and Lamming, 2016; López-Otín et al., 2023).

5.1. Clinical Evidence for Diet-Related Intervention Effectiveness

Two significant challenges complicate the analysis of molecular pathways in human Randomized Controlled Trials (RCTs): the difficulty in maintaining adherence to strict regimens (e.g., long-term CR) and the ethical limitations on tissue sampling (Anderson and Weindruch, 2012). Regarding modulation of the pathway, data from the CALERIE and other human studies demonstrate that mild CR in healthy adults results in measurable effects, including reductions in IGF-1 and improvements in cardiometabolic risk factors (Kraus et al., 2019). This decrease in growth factors is an indirect marker of downregulation of the given pathway (Fontana and Partridge, 2019). Also, clinical data with the Fasting-Mimicking Diet (FMD) have shown significant improvements in markers and risk factors for aging (Wei et al., 2017). These protocols also induce multi-system regeneration (Brandhorst et al., 2015) and have positive effects on specific molecular markers of aging (Longo et al., 2021). However, a significant translational gap remains between the remarkable potencies achievable with pharmacological agents (such as rapamycin targeting mTOR in mice) and the more subtle, yet sustainable, effects on the overall biosphere of the complex human organism achievable through nutritional interventions. In addition to diet, researchers are investigating other lifestyle factors that affect telomere length and cancer risk, as well as pharmacologic agents (Shammas, 2011). For example, senolytic agents are advancing from discovery to translation by targeting cellular senescence pathways that overlap with those associated with dietary benefits (Kirkland and Tchkonia, 2020).

5.2. Epigenetic Clocks and the Impact of Diet

To objectively assess whether an intervention decelerates aging, researchers are turning to novel biomarkers of aging and cellular homeostasis (Kennedy and Lamming, 2016). Among these, the epigenetic clock (based on DNA methylation patterns) is considered the most accurate predictor of biological age, often surpassing chronological age (Horvath and Raj, 2018). This model, based on genome-wide methylation profiles (Hannum et al., 2013), is currently being validated as a tool to track the effects of interventions. This concept is illustrated visually in Figure 3.

Based on recent clinical findings, dietary and lifestyle changes appear to delay, or even halt, rapid biological aging when epigenetic modulation is considered. Researchers have recently confirmed at least one new epigenetic biomarker (PhenoAge) that predicts both healthspan and lifespan (Levine et al., 2018). Meta-analyses show that lifestyle interventions (diet and exercise) impact epigenetic clocks. At the molecular level, these changes serve as objective parameters for assessing the effects of different lifestyle interventions (Quach et al., 2023).

5.3. Multi-Omics and Precision Longevity

The future of dietary intervention lies in Precision Longevity Medicine, which relies on multi-omics data (genomics, proteomics, metabolomics). The metabolomics of human aging presents new advances and opportunities for identifying effective interventions. Specifically, as a small-molecule profiling technology, metabolomics can identify molecular signatures of longevity and aging by

analyzing biological fluids. Studies show that Intermittent CR modulates metabolic and immune parameters in humans (Fitzgerald et al., 2022), indicating that scientists can predict the dietary signals. In terms of personalization, using such data will enable moving from generic recommendations (e.g., "limit calories") to patient-specific advice that predicts which individuals will respond best to an IF regimen rather than a MedDiet, based on their genetic and metabolic profiles.

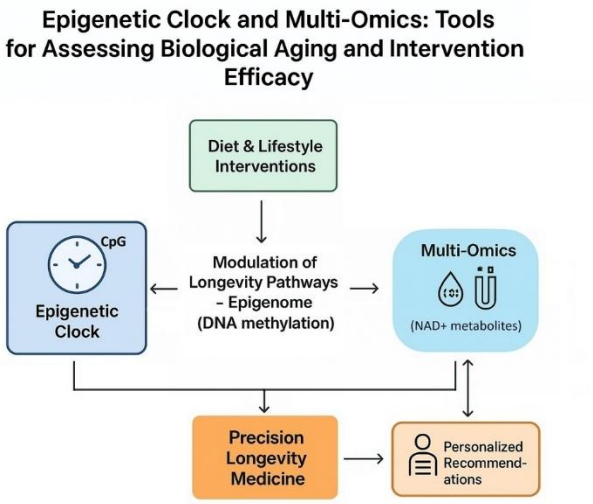

Figure 3. The figure demonstrates the concept of biological age assessment. Lifestyle (Diet, Exercise) influences molecular pathways (mTOR, Sirtuins) that act on the Epigenome (DNA methylation patterns). The Epigenetic Clock provides an objective measure of the resulting biological age. Multi-Omics techniques (Metabolomics, Proteomics) monitor intermediate molecular signatures (such as NAD+ metabolites, amino acid levels) that inform or associate with the effectiveness of personalized treatments (Based on ideas from Horvath and Raj, 2018; Barzilai and Cohen, 2022).

6. FUTURE PROSPECTS

6.1. Synthesis of Key Findings

This review explains that making changes to diet and lifestyle is not just about looking good, but a major way to change the way our bodies work at the most basic level as we age. Diet and lifestyle modifications can influence the metabolism of aging and of cell proliferation and repair. Other mechanisms by which diet and lifestyle modifications support cellular and metabolic functions of the body include modulation of AMPK and Sirtuins and inhibition or attenuation of mTOR-mediated anabolic signaling. In addition, complex dietary patterns (e.g., the MedDiet) are protective via multiple mechanisms, such as reduced exposure to inflammaging and beneficial modulation of the gut microbiome (Mazza et al., 2021; Sanz et al., 2020).

6.2. Knowledge Gaps and Panoramas of the Future

Although researchers have made substantial advances, many critical knowledge gaps impede the full translation of these findings into the clinic.

The optimal dose, timing, and duration of IF or CR in humans remain a matter of debate. In the future, studies should use multi-omics data (such as metabolomics and proteomics) to design personalized interventions based on endogenous molecular patterns that distinguish responders from non-responders. This imperative for personalization also applies to food composition, as differences in protein source and amount influence critical aspects of longevity signaling (Brandhorst and Longo, 2019), further complicating personalized dietary advice. Furthermore, regarding tissue specificity, most of the mechanisms understood today are quite general. Research will also need to investigate how interventions may differentially influence these longevity pathways across various human tissues (e.g., brain, muscle, adipose tissue), particularly in light of integrated lifestyle factors and inter-organ crosstalk (Safdar et al., 2016). In terms of validation with biomarkers, while the epigenetic clock has emerged as a promising tool (Levine et al., 2018), investigators must conduct more extensive and long-term RCTs to validate its ability—and the ability of other biomarkers—to reliably track the efficacy of nutritional and lifestyle changes in clinical settings (Kirkland and Tchkonia, 2020). Additionally, scientists must further examine the impact of diet on the microenvironment surrounding senescent cells and their role in cancer and aging (Campisi,

2013). Finally, regarding microbiome-pathway crosstalk, researchers must further investigate how gut microbiota metabolites (i.e., SCFAs) directly signal and influence central host longevity pathways, such as mTOR and Sirtuins (O'Toole and Jeffery, 2015).

7. CONCLUSION

In conclusion, a holistic understanding of the Impact of Diet and Lifestyle on the Aging Process—integrating molecular mechanisms, interactions, and translational biomarkers—is essential. The future of geriatric medicine lies in implementing these findings to maximize the human healthspan and reduce the burden of age-related diseases.

Acknowledgments

We thank the authors who contributed to the conduct of this study.

Authors' Contributions

Zuzanna Zgrzywa: Conceptualization; Project Administration; Writing—Original Draft Preparation (Introduction and Conclusion); Supervision.
Brygida Tucka: Methodology Development; Writing—Original Draft Preparation (Core Molecular Pathways).
Jakub Szyszkowski: Formal Analysis; Critical Review of Molecular Pathway Assessment.
Izabella Zawadzka: Literature Search and Data Curation (Dietary Strategies).
Paulina Wądołowksa: Literature Search and Data Curation (Integration and Synergy).
Bartłomiej Kowalski: Literature Search and Data Curation (Translational Impact); Data Visualization Support.
Natalia Kriese: Validation; Writing—Original Draft Preparation (Translational Impact).
Ewelina Komorowska: Writing—Review and Editing (Sections 1, 2, and 3); Visualization.
Jakub Jaworski: Writing—Review and Editing (Sections 4, 5, and 6); Critical Review.
Tomasz Kucharski: Conceptualization; Final Manuscript Review and Approval.
All authors have read and agreed to the published version of the manuscript.

Informed consent

Not applicable.

Ethical approval

Not applicable. This article does not contain any studies with human participants or animals performed by any of the authors.

Funding

This research did not receive any external funding like specific grant from funding agencies in the public, commercial, or nonprofit sectors.

Conflict of interest

The authors declare that they have no conflicts of interest, competing financial interests or personal relationships that could have influenced the work reported in this paper.

Data and materials availability

All data associated with this work are present in the paper.

REFERENCES

1. Anderson RM, Weindruch R. The caloric-restriction paradigm: implications for healthy human aging. Am J Hum Biol 2012; 24: 101–106.
2. Barrès R, Yan J, Egan B, Treebak JT, Rasmussen M, Fritz T, Caidahl K, Krook A, O'Gorman DJ, Zierath JR. Acute exercise remodels promoter methylation in human skeletal muscle. Cell Metab 2012; 15: 405–411.
3. Barzilai N, Cohen P. The promise of metabolomics in identifying effective longevity interventions. Cell Metab 2022; 34: 663–674.

4. Brandhorst S, Choi IY, Wei M, Cheng CW, Sedrakyan S, Navarrete G, Dubeau L, Yap LP, Park R, Vinciguerra M, Di Biase S, Mirzaei H, Mirisola MG, Childress P, Ji L, Groshen S, Penna F, Odetti P, Perin L, Conti PS, Ikeno Y, Kennedy BK, Cohen P, Morgan TE, Dorff TB, Longo VD. A periodic diet that mimics fasting promotes multi-system regeneration, enhanced cognitive performance, and healthspan. Cell Metab 2015; 22: 86–99.
5. Brandhorst S, Longo VD. Protein quantity and source, fasting-mimicking diets, and longevity. Adv Nutr 2019; 10: S340–S350.
6. Campisi J. Aging, cellular senescence, and cancer. Annu Rev Physiol 2013; 75: 685–705.
7. Cantó C, Houtkooper RH, Pirinen E, Youn DY, Oosterveer MH, Cen Y, Fernandez-Marcos PJ, Yamamoto H, Andreux PA, Cettour-Rose P, Gademann K, Rinsch C, Schoonjans K, Sauve AA, Auwerx J. The NAD+ precursor nicotinamide riboside enhances oxidative metabolism and protects against high-fat diet–induced obesity. Cell Metab 2012; 15: 838–847.
8. Cantó C, Menzies KJ, Auwerx J. NAD+ metabolism and the control of energy homeostasis: a balancing act between mitochondria and the nucleus. Cell Metab 2015; 22: 31–53.
9. Cienfuegos S, Gabel K, Kalam F, Ezpeleta M, Wiseman E, Pavlou V, Lin S, Oliveira ML, Varady KA. Effects of time-restricted feeding on glycemic control and metabolic health in humans: a systematic review. Rev Endocr Metab Disord 2021; 22: 325–337.
10. de Cabo R, Mattson MP. Effects of intermittent fasting on health, aging, and disease. N Engl J Med 2019; 381: 2541–2551.
11. Fang P, She Y, Yu M, Yu Y, Yu L, Zhang C. Adipose-muscle crosstalk in age-related metabolic disorders: mechanisms and potential interventions. Ageing Res Rev 2023; 84: 101829.
12. Fitzgerald KC, Brooks J, Davis M, Smith M, Jones A, Mowry EM. Intermittent calorie restriction alters T-cell subsets and metabolic markers in people with multiple sclerosis. EBioMedicine 2022; 82: 104124.
13. Fontana L, Partridge L. Dietary protein, IGF-1, mTOR and aging: mechanistic links and human evidence — review. Nat Rev Endocrinol 2019; 15: 459–471.
14. Gomez-Cabrera MC, Domenech E, Romagnoli M, Arduini A, Borras C, Pallardo FV, Sastre J, Viña J. Exercise as an antioxidant: it upregulates important enzymes for cellular adaptations to exercise. Br J Sports Med 2012; 46: 250–256.
15. Guarente L. Calorie restriction and sirtuins: the search for conserved metabolic signals. Cell Metab 2015; 21: 686–695.
16. Handschin C, Spiegelman BM. The role of exercise-induced myokines in inter-organ crosstalk during caloric restriction. Science 2020; 368: eaba6125.
17. Hannum G, Guinney J, Zhao L, Zhang L, Hughes G, Sadda S, Klotzle B, Bibikova M, Fan JB, Gao Y, Deconde R, Chen M, Rajapakse I, Friend S, Ideker T, Zhang K. Genome-wide methylation profiles reveal quantitative views of human aging rates. Mol Cell 2013; 49: 359–367.
18. Hardie DG, Ross FA, Hawley SA. AMPK: a nutrient and energy sensor that maintains energy homeostasis. Nat Rev Mol Cell Biol 2012; 13: 251–262.
19. He C, Bassik MC, Moresi V, Sun K, Wei Y, Zou Z, An Z, Loh J, Fisher J, Sun Q, Korsmeyer S, Packer M, May HI, Hill JA, Virgin HW, Gilpin C, Xiao G, Bassel-Duby R, Scherer PE, Levine B. Exercise and regulation of autophagy in skeletal muscle. Autophagy 2012; 8: 1266–1278.
20. Heilbronn LK, Ravussin E. Calorie restriction and aging: review of the literature and implications for studies in humans. Am J Clin Nutr 2017; 105: 1017–1025.
21. Horvath S, Raj K. DNA methylation-based biomarkers and the epigenetic clock. Nat Rev Genet 2018; 19: 371–384.
22. Kennedy BK, Lamming DW. The mechanisms of aging and the decline in cellular homeostasis. Cell 2016; 166: 1004–1017.
23. Kenyon C. The genetics of aging. Nature 2010; 464: 504–512.
24. Kirkland JL, Tchkonia T. Senolytic drugs: from discovery to translation. J Intern Med 2020; 288: 518–536.
25. Kraus WE, Bhapkar M, Huffman KM, Pieper CF, Krupa Das S, Redman LM, Villareal DT, Rochon J, Roberts SB, Ravussin E, Holloszy JO, Fontana L. Two years of caloric restriction and cardiometabolic risk: exploratory outcomes of the CALERIE phase 2 randomized controlled trial. Lancet Diabetes Endocrinol 2019; 7: 673–685.
26. Levine ME, Lu AT, Quach A, Bhushan A, Belsky DW, Martino D, Riley BP, Maecker HT, Mitsunaga E, Gao W, Smith AS, Snyder-Mackler N, Horvath S. An epigenetic biomarker of aging for lifespan and healthspan. Aging (Albany, NY) 2018; 10: 573–591.
27. Levine ME, Suarez JA, Brandhorst S, Balasubramanian P, Cheng CW, Madia F, Fontana L, Mirisola MG, Guevara-Aguirre J, Wan J, Passarino G, Kennedy BK, Wei M, Cohen P, Crimmins EM, Longo VD. Low protein intake is associated with a major reduction in IGF-1, cancer, and overall mortality in the 65 and younger but not older population. Cell Metab 2014; 19: 407–417.
28. Longo VD, Brandhorst S. The effect of fasting and caloric restriction on aging and longevity: a perspective. Nat Rev Mol Cell Biol 2020; 21: 492–506.
29. Longo VD, Fabbiano S, Brandhorst S, Wei M, Cheng CW. Fasting-mimicking diet and molecular markers of aging: clinical and mechanistic studies. Cell Metab 2021; 33: 1870–1884.

30. Longo VD, Panda S. Fasting, circadian rhythms, and metabolic health. Annu Rev Nutr 2016; 36: 371–394.
31. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. Hallmarks of aging: An expanding universe. Cell 2023; 186: 243–278.
32. Mattson MP, Longo VD, Harvie M. Impact of intermittent fasting on health and disease processes. Ageing Res Rev 2017; 39: 46–58.
33. Mazza E, Zupo R, Castellana F, Sardone R, Lampignano L, Paradiso S, Giannelli G. Mediterranean diet in healthy aging: a review. J Gerontol A Biol Sci Med Sci 2021; 76: 1735–1745.
34. O'Toole PW, Jeffery IB. Gut microbiota and aging. Science 2015; 350: 1214–1215.
35. Pedersen BK, Febbraio MA. Muscles, exercise and obesity: skeletal muscle as a secretory organ. Nat Rev Endocrinol 2012; 8: 457–465.
36. Quach A, Levine ME, Tanaka T, Lu AT, Chen BH, Ferrucci L, Ritz B, Bandinelli S, Neuhouser ML, Beasley JM, Snetselaar L, Wallace RB, Tsao PS, Absher D, Assimes TL, Stewart JD, Li Y, Hou L, Baccarelli AA, Whitsel EA, Horvath S. Impact of lifestyle factors on epigenetic clocks: a systematic review. Aging Cell 2023; 22: e13955.
37. Safdar A, Saleem A, Tarnopolsky MA. Exercise-induced myokines and inter-organ crosstalk. J Appl Physiol 2016; 120: 446–458.
38. Sanz JM, Rastrello A, Romani A, Passaro A. The role of polyphenols in modulating the gut microbiota and promoting healthspan. Oxid Med Cell Longev 2020; 2020: 8931589.
39. Shammas MA. Telomeres, lifestyle, cancer, and aging. Curr Opin Clin Nutr Metab Care 2011; 14: 28–34.
40. Sillanpää E, Mäkinen P, Rinne JO, Kujala UM, Kaprio J. Blood and skeletal muscle ageing determined by epigenetic clocks and their associations with lifestyle. Clin Epigenetics 2021; 13: 143.
41. Solon-Biet SM, McMahon AC, Ballard JW, Ruohonen K, Wu LE, Cogger VC, Warren A, Huang X, Pichaud N, Melvin RG, Gokarn R, Khalil M, Turner N, Cooney GJ, Sinclair DA, Raubenheimer D, Le Couteur DG, Simpson SJ. The ratio of macronutrients, not caloric intake, dictates cardiometabolic health and longevity. Cell Metab 2014; 19: 418–430.
42. Timmers S, Konings E, Bilet L, Houtkooper RH, van de Weijer T, Goossens GH, Hoeks J, van der Krieken S, Ryu D, Kersten S, Moonen-Kornips E, Hesselink MKC, Kunz I, Schrauwen-Hinderling VB, Blaak E, Auwerx J, Schrauwen P. Calorie restriction-like effects of resveratrol on energy metabolism and mitochondrial function in humans. Cell Metab 2011; 14: 612–622.
43. van der Velpen V, Teav T, Gallart-Ayala H, Ivanisevic J. Role of NAD^+ precursors in mitochondrial function and metabolic health. Ageing Res Rev 2022; 77: 101649.
44. Vargas-Ortiz K, Pérez-Vázquez V, Macías-Cervantes MH. Exercise and sirtuins: pathways linking physical activity to mitochondrial health in skeletal muscle. Int J Mol Sci 2019; 20: 2717.
45. Wei M, Brandhorst S, Shelehchi M, Mirzaei H, Cheng CW, Budniak J, Groshen S, Hwang WJ, Haleyley N, Bacciocco P, Cohen P, Longo VD. Fasting-mimicking diet and markers/risk factors for aging, diabetes, cancer and cardiovascular disease: clinical trial results. Sci Transl Med 2017; 9: eaai8700.
46. Welton S, Minty R, O'Driscoll T, Willms H, Poirier D, Madden S, Kelly L. Intermittent fasting and weight loss: systematic review. Nutrients 2020; 12: 2568.
47. Wilkinson MJ, Manoogian ENC, Zadourian A, Lo H, Fakhouri S, Shoghi A, Wang X, Fleischer JG, Navlakha S, Panda S, Taub PR. Ten-hour time-restricted eating reduces weight, blood pressure, and atherogenic lipids in patients with metabolic syndrome. Cell Metab 2020; 31: 92–104.e5.
48. Zierer J, Kastenmüller G, Suhre K, Gieger C, Curoczi J, Peters A, Waldenberger M. Integrated systems analysis reveals coordinated metabolic and epigenetic responses to exercise training. Cell Metab 2015; 22: 1048–1059.
49. Zoncu R, Efeyan A, Sabatini DM. mTOR: a master regulator of cell growth and division. Curr Opin Cell Biol 2011; 23: 137–146.