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REVIEW ARTICLE

Organoids in aging research: Decoding mechanisms, accelerating interventions, and bridging translation

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(This article belongs to the *Special Issue: Organoids and Aging Research: From Model Construction to Anti-Aging Interventions*)

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Citation: Yang Y, Wang Y, Yin H, *et al*. Organoids in aging research: Decoding mechanisms, accelerating interventions, and bridging translation. *Organoid Res.* 2025;1(4):025450032. doi: 10.36922/OR025450032

Received: November 5, 2025

Revised: December 12, 2025

Accepted: December 16, 2025

Published online: December 30, 2025

Abstract

Aging, as a process of gradual decline in cellular and tissue function, poses a major challenge for healthcare systems worldwide. However, traditional models (experimental animals and 2D cell cultures) struggle to reproduce the complexity of human aging, which limits the depth of mechanistic understanding. Organoids, defined as self-organizing 3D stem cell-derived structures that replicate key organ features, have effectively addressed this research gap. This article reviews the applications of organoids in the study of aging, including their core principles, methods for generating common organoid types, advantages, and limitations. The validation processes and mechanisms of the aging model are also discussed. In addition, the applications of brain organoids in research on Alzheimer's disease and Parkinson's disease, heart organoids in research on myocardial aging, and liver and islet organoids in research on diabetes are emphasized. Despite advances in single-cell sequencing, gene editing, and imaging technologies, challenges such as standardization and vascularization remain. Nevertheless, organoids have accelerated the development of anti-aging drugs and personalized medicine, thus becoming indispensable tools for understanding the mechanisms of human aging and developing interventions to extend healthy life span.

Keywords: Age-related diseases; Aging; Mechanisms; Organoids; Translation

1. Introduction

Aging is a complex physiological process that can have a profound impact on physical health and daily quality of life. As the global population ages, aging research is becoming increasingly important. According to the World Health Organization projections, 22% of the world's population will be over 60 years old by 2050.[1] Population aging poses multiple serious challenges, including shortages of medical resources, increased pension burdens, and reduced quality of life among the elderly.[2] Therefore, in-depth research on the mechanisms of aging is not only the core topic in the field of life sciences but also a necessary prerequisite for addressing the challenges of an aging society.[3]

The risk of developing a variety of chronic diseases increases significantly with age, including cardiovascular disease, neurodegenerative disease, cancer, and diabetes.

More than 70% of deaths among people over 65 years of age are related to these age-related diseases, including cardiovascular and cerebrovascular diseases and all types of cancer.[4-6] These diseases not only seriously threaten the longevity and health of older individuals but also place considerable pressure on the healthcare system and social support resources. Therefore, it is necessary to investigate in depth the molecular and cellular changes that occur during aging to reveal the mechanisms underlying disease onset and progression and to provide a theoretical basis for the development of effective prevention and treatment strategies.[7] For instance, clarifying the relationship between endothelial dysfunction and cardiovascular diseases provides opportunities to prevent or delay disease onset and promote functional recovery.[8,9] In addition, aging research is of great significance for improving the quality of life and extending the healthy life span of older adults. By elucidating the biological mechanisms of aging and exploring effective intervention strategies, such as anti-aging drugs and lifestyle interventions, advances in science and technology can help older individuals maintain physical and mental health, reduce disease incidence and functional decline, and ultimately achieve healthy aging.[10-12]

Organoids have attracted increasing attention due to their high structural and functional similarity to native tissues/organs, diverse sources, broad applicability, strong individual specificity, and comparative experimental accessibility.[13] Although they cannot fully reproduce the complexity and integrity of native organs, organoids can recapitulate key aspects of cellular composition, cell–cell interactions, and spatial organization to a significant extent.[14] For example, intestinal organoids can form crypt–villus structures and exhibit nutrient absorption and secretory functions[15-17]; while liver organoids are capable of drug metabolism and protein synthesis.[18,19] Organoids can be derived from embryonic stem cells, induced pluripotent stem cells (iPSCs), adult stem cells, and tumor tissues, making them versatile tools across biomedical research. These characteristics enable organoids to play important roles in developmental biology, disease modeling, drug screening, and regenerative medicine. Moreover, the use of patient-derived cells allows for personalized research and treatment strategies, facilitating gene editing, drug testing, and mechanistic studies of organ development and disease progression.[20-24] The advantages and limitations of organoid models compared with traditional cell and animal models are summarized in Figure 1.

The advent of organoid technology represents a significant advance in the field, providing the capacity to model complex and dynamic physiological processes, including organogenesis, cellular senescence, and tissue regeneration. By constructing organoid models from different tissue origins, sources, and even developmental stages, researchers can observe dynamic cellular and tissue changes during aging that were previously difficult to study. These changes include decreased proliferative capacity, altered metabolic function, and disrupted cell–cell interactions.[25,26] Brain organoid aging models enable investigation of how neural stem cell aging affects neuronal differentiation and function, as well as the abnormal aggregation of neurodegeneration-related proteins and the initiation and progression of neuroinflammation.[27-31] In addition, organoid technology offers powerful tools for elucidating the molecular mechanisms underlying aging. Gene-editing technologies allow inactivation or overexpression of pivotal genes, facilitating investigation of their roles in aging-associated signaling pathways and enabling identification of critical regulators and downstream targets.[25,32,33] For example, knocking out aging-related genes in liver organoids using clustered regularly interspaced short palindromic repeats (CRISPR)–CRISPR-associated protein 9 (Cas9) technology and monitoring hepatocyte senescence and metabolic alterations can help uncover liver-specific aging mechanisms and identify potential targets for anti-aging interventions.[34,35]

A clearer positioning of organoid systems relative to conventional 2D cultures and animal models helps contextualize their expanding role in disease modeling. Unlike 2D monolayers, which lack spatial organization and lineage diversity, organoids recreate essential aspects of human tissue architecture, including cytoarchitecture, multicellular patterning, and region-specific differentiation. These features enable emergent properties—such as neuronal circuit formation, metabolic zonation, and epithelial barrier organization—that cannot arise in flat cultures.[13] Compared with animal models, organoids provide a uniquely human biological context, capturing species-specific transcriptional programs, signaling dynamics, and disease-related gene regulation that frequently diverge from murine physiology. Such fidelity is particularly important for modeling neurodegenerative and age-related disorders, in which developmental trajectories, immune responses, and metabolic pathways differ substantially between humans and rodents. However, organoids also possess intrinsic limitations that distinguish them from both 2D and *in vivo* systems. The absence of functional vasculature limits the accurate reproduction of blood flow-dependent transport, metabolic gradients, and hemodynamic cues, while the lack of a complete immune system restricts the modeling of systemic inflammation, microglial diversity, and immune cell interactions.[36] Moreover, organoids cannot fully replicate organism-level physiology, including hormonal regulation, interorgan communication, and long-range neural connectivity. Thus, organoids occupy an intermediate position between simplified cell cultures and complex *in vivo* systems, offering unprecedented access to

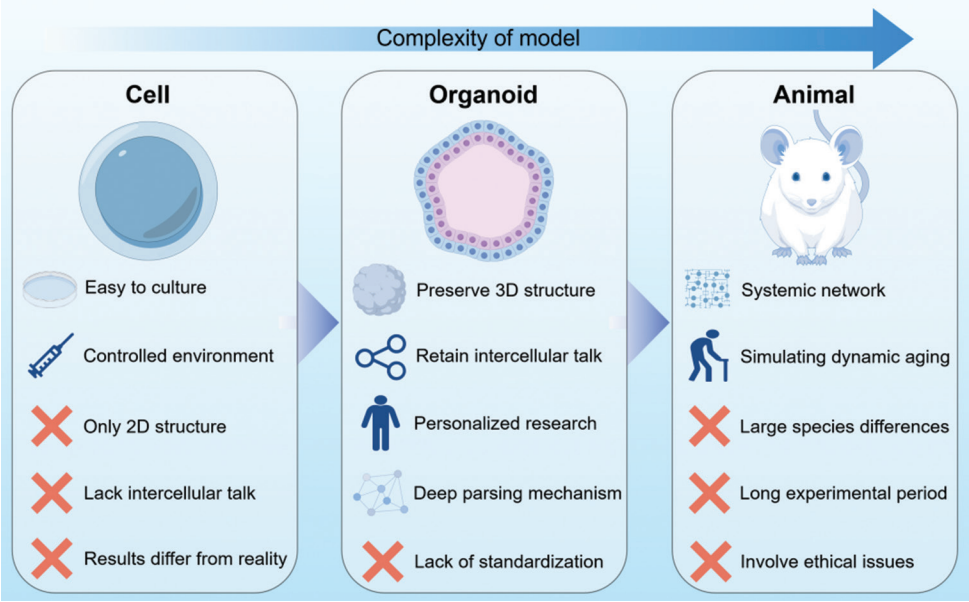

Figure 1. Organoids as an emerging model system for studying aging mechanisms and age-related diseases. Created with Figdraw 2.0.

human-specific biology while requiring integration with complementary approaches, such as microfluidic platforms, vascularized scaffolds, and immune co-culture systems, to overcome current constraints.

The purpose of this review is to examine the value of organoids in aging research, a field long constrained by the limitations of traditional models in recapitulating the complexity of human aging. We discuss the core principles of organoids, their roles in elucidating cellular and tissue aging mechanisms, and their applications in age-related disease research and anti-aging drug development. This review aims to provide insights into how organoids can bridge basic aging biology and clinical translation, addressing an urgent need in an increasingly aging global society.

2. Methods

2.1. Literature search strategy

To enhance methodological transparency and enhance the scientific rigor of this narrative review, a structured literature search was conducted across multiple biomedical databases. Searches were performed in PubMed, Web of Science, Scopus, and Google Scholar between January 2000 and October 2025. A combination of controlled vocabulary terms and free-text keywords was used, including but not limited to: "organoid," "brain organoid," "cerebral organoid," "aging," "senescence," "cellular senescence," "neurodegeneration," "Alzheimer's disease," "Parkinson's disease," "age-related diseases," "stem-cell derived organoids," "disease modeling," "single-cell sequencing," "gene editing," and "organ-on-chip." Boolean operators (AND/OR) were applied to refine search specificity (e.g., organoid AND aging, brain organoid OR cerebral organoid, senescence AND neurodegeneration).

2.2. Inclusion criteria

To ensure the relevance, quality, and consistency of the literature included in this review, studies were selected based on the following predefined inclusion criteria: (i) Peer-reviewed original research articles, reviews, or methodological papers published in English; (ii) studies employing organoid or organoid-derived systems to investigate aging, cellular senescence, neurodegeneration, or molecular mechanisms relevant to age-associated disorders; (iii) articles reporting mechanistic findings, technological advancements, or translational applications of organoid models; and (iv) human- or mouse-derived organoids, including iPSC-derived systems.

2.3. Exclusion criteria

Studies were excluded from this review if they met any of the following criteria, which were defined to eliminate irrelevant, low-quality, or methodologically unsuitable publications: (i) Studies based solely on 2D cell culture or animal models without organoid involvement; (ii) conference abstracts, editorials, or commentaries without original scientific data; (iii) reports lacking mechanistic relevance to aging or disease modeling; and (iv) non-English publications.

The reference lists of all included studies were manually screened to identify additional relevant publications not captured by the initial database queries. All retrieved articles were independently reviewed by two authors to

minimize selection bias. Discrepancies were resolved through discussion and consensus, ensuring comprehensive coverage of the current state of organoid-based aging research.

3. Principles and preparation of organoid technology

3.1. Basic principles of organoids

The capacity of stem cells for self-renewal, proliferation, and differentiation forms the cornerstone of organoid construction.[37] Stem cells are undifferentiated cells with the potential to self-renew and differentiate into multiple specialized cell types under appropriate conditions. In most established organoid platforms, stem cells serve as the foundational units, providing the fundamental driving force for simulating organ development and function *in vivo*.[38,39]

Self-renewal is a key feature that enables stem cells to maintain population stability. In organoid culture, the continuous generation of new cells through mitotic division is essential for sustaining the stem cell pool and supporting organoid growth and development. This process is tightly regulated by intrinsic gene regulatory networks and extrinsic signaling pathways.[40,41] The wingless-related integration site (Wnt) signaling pathway plays a central role in the self-renewal of intestinal stem cells by activating genes associated with cell proliferation and stemness maintenance.[42,43] In intestinal organoid cultures, the addition of Wnt pathway agonists promotes sustained stem cell proliferation, thereby providing sufficient cellular resources for organoid formation.[44]

Cell differentiation refers to the process by which stem cells develop into specialized cell types, enabling organoids to form functionally diverse cell populations that mimic native organ structure and function. During differentiation, stem cells are influenced by multiple factors, including cytokines, the extracellular matrix (ECM), and cell–cell interactions, which collectively guide lineage specification. In liver organoid formation, stem cells differentiate into liver-specific cell types, such as hepatocytes and cholangiocytes, typically through supplementation with growth factors including hepatocyte growth factor and fibroblast growth factor.[45] These cells are spatially organized within a 3D structure, ultimately forming liver organoids that exhibit key hepatic functions, such as metabolism and detoxification.[46]

The self-organization capability of organoids represents an important mechanism in the formation of organ-specific architectures. Within appropriate 3D culture environments, stem cells and their differentiated progeny can spontaneously assemble into multicellular structures with defined spatial organization and function. This self-organizing process arises from cell–cell recognition, interactions, and responses to microenvironmental cues.[47] For example, in the presence of ECM components and defined growth factors, neural stem cells self-organize into cerebral cortical-like organoids containing multiple neuronal and glial layers, and recapitulating key aspects of brain development such as neurogenesis, neuronal migration, and differentiation.[29] Common signaling pathways involved in the construction of germ layer-derived organoids and aging-related research are shown in Figure 2.

3.2. Generation of common organoids

3.2.1. Brain organoids

Human pluripotent stem cells, including embryonic stem cells and iPSCs, are commonly utilized as starting cells for the preparation of brain organoids. First, iPSCs are induced to initiate differentiation, leading to their transformation into neuroectodermal cells. During this process, specific small molecule compounds and cytokines, such as the transforming growth factor-β signaling pathway inhibitor SB431542 and glycogen synthase kinase 3β (GSK-3β) inhibitor CHIR99021, which activates the Wnt signaling pathway, are added to promote the differentiation of stem cells into neuroectoderm.[48] Subsequently, neuroectodermal cell aggregates are embedded in Matrigel and cultured in suspension using a rotary bioreactor or low-adherence culture dishes. During culture, nutrients and signaling molecules needed for brain development, such as retinoic acid and brain-derived neurotrophic factor (BDNF), are added sequentially to guide further differentiation and self-organization of the cell aggregates, ultimately forming brain organoids with characteristics of distinct brain regions.[49,50] These organoids not only contain neurons, astrocytes, and other neural cell types but also exhibit layered structures resembling the cerebral cortex and display rudimentary brain electrophysiological activity.[27,31,38,41,48]

3.2.2. Heart organoids

Recent advances in cardiac organoid fabrication have achieved unprecedented levels of biomimicry through the integration of bioengineering strategies. A pioneering protocol employs human iPSCs undergoing stepwise activation of six embryonic cardiac developmental signaling pathways,[51] enabling scaffold-free self-organization into beating organoids with spontaneous cavity formation and injury-responsive fibroblast migration.[52] Advanced 3D bioprinting using microscale continuous optical printing technology now allows nanoscale-precision deposition of iPSC-derived cardiomyocytes and endothelial cells within GelMA hydrogels, achieving anisotropic myofiber alignment that closely mimics native myocardial architecture.[53] Serum-free differentiation systems further standardize production, generating electrophysiologically

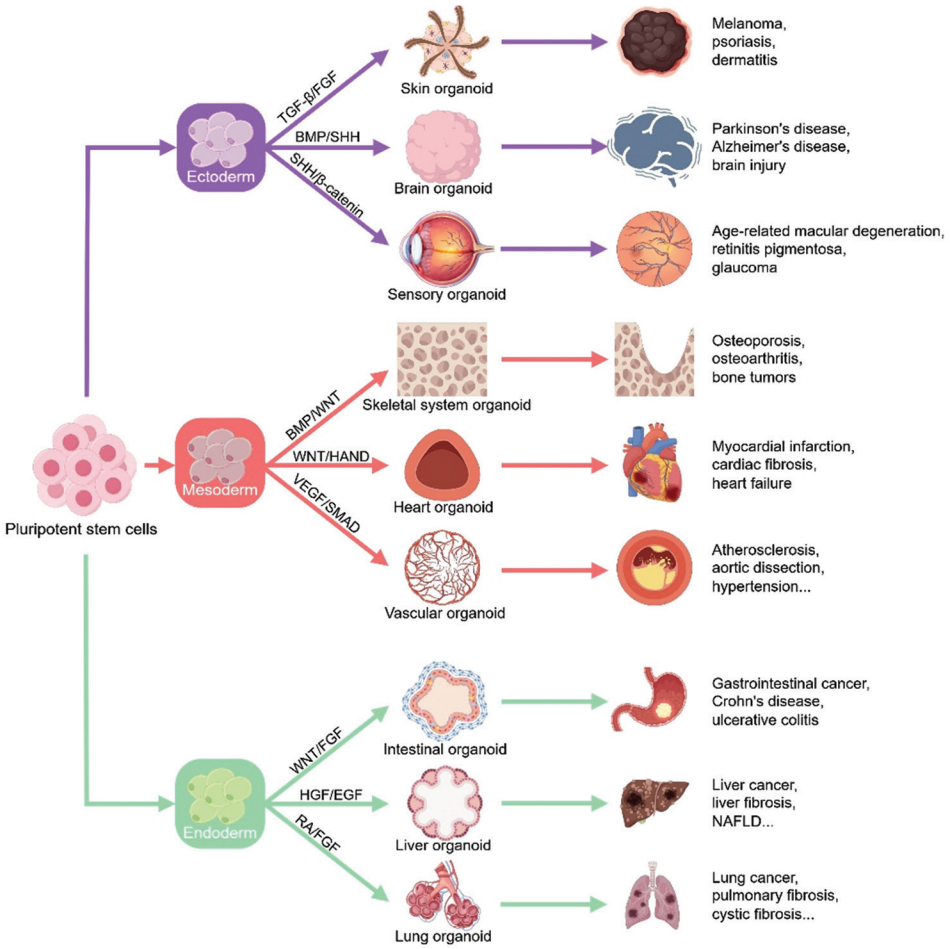

Figure 2. Representative organoid preparation pathways and research applications. Created with Figdraw 2.0.
Abbreviations: BMP: Bone morphogenetic protein; EGF: Epidermal growth factor; FGF: Fibroblast growth factor; HAND: Heart and neural crest derivatives; HGF: Hepatocyte growth factor; NAFLD: Nonalcoholic fatty liver disease; RA: Retinoic acid; SHH: Sonic hedgehog; TGF-β: Transforming growth factor-β; VEGF: Vascular endothelial growth factor

functional cardiac organoids responsive to pharmacological agents such as isoproterenol within 7–13 days.[54] Dynamic culture in rotating wall vessel bioreactors enhances organoid viability and thickness while upregulating cardiac maturation markers connexin 43 and myosin heavy chain 7.[55-57] Single-cell sequencing analyses have identified *ETS1* as a critical regulator of cardiac lineage commitment, thereby improving differentiation efficiency. Collectively, these innovations enable the generation of centimeter-scale cardiac organoids with synchronized contractions and drug-responsive electrophysiological properties, bridging important gaps in disease modeling and regenerative medicine.[58,59]

3.2.3. Liver organoids

Liver organoids can be generated using two main approaches: Liver progenitor cells isolated from human or animal liver tissue,[60] or hepatocyte-like cells derived from iPSCs.[61] To obtain liver progenitor cells, liver tissue is minced and enzymatically digested using enzymes such as trypsin and collagenase to dissociate single cells, after which liver progenitor cells are enriched by flow cytometry. These cells are then mixed with ECM-containing hydrogels and seeded into culture dishes.[62] Following hydrogel solidification, culture medium supplemented with hepatocyte growth factor, fibroblast growth factor, dexamethasone, and other growth factors and hormones is added.[45] These factors promote the proliferation and differentiation of hepatic progenitor cells, resulting in liver organoids containing hepatocytes, cholangiocytes, and other cell types that recapitulate key hepatic functions, including metabolism and detoxification.[63,64] For iPSC-derived liver organoids, iPSCs are first differentiated into definitive endoderm and subsequently into hepatocyte-like cells. The subsequent culture and maturation processes are largely similar to those used for liver progenitor cell-derived organoids.[65]

4. Establishment of organoid models for aging research

4.1. Strategies for constructing aging models based on organoids

Strategies for constructing organoid-based aging models mainly focus on two core approaches: Inducing stem cell differentiation and simulating aging-related signaling pathways.[66] In differentiation-based aging models, researchers exploit the pluripotency of stem cells and drive them toward senescence by inducing their differentiation into tissue-specific organoids under specific culture conditions and differentiation cues. Figure 3 illustrates the general workflow for generating human organoids in aging-related studies. Using neural stem cells as an example, reducing the concentration of growth factors during differentiation and culture, such as decreasing levels of BDNF and nerve growth factor, can impair proliferative capacity and differentiation efficiency, thereby promoting the entry of cells into an aging-like state.[67,68] Additionally, exposure to defined concentrations of hydrogen peroxide can simulate an oxidative stress environment and accelerate the development of senescent phenotypes in neural organoids.[69] These approaches provide valuable experimental models for investigating the mechanistic links between neurodegenerative diseases and aging.

Simulation of senescence-related signaling pathways represents another key strategy for constructing organoid aging models. Numerous signaling pathways have been identified as critical regulators of aging, and modulation of these pathways can induce aging-related phenotypes in organoids. The Wnt/β-catenin signaling plays a pivotal role in regulating cell proliferation, differentiation, and senescence. In intestinal organoid cultures, inhibition of Wnt signaling using inhibitor of Wnt Production-2 (IWP-2) reduces intestinal stem cell proliferation and induces cell cycle arrest, resulting in aging-associated phenotypes.[70] These changes include altered cell morphology, decreased expression of the proliferation marker Ki-67, and increased activity of senescence-associated β-galactosidase (SA-β-gal). The mechanistic target of rapamycin (mTOR) signaling pathway is also closely linked to aging. In liver organoid cultures, treatment with rapamycin inhibits mTOR signaling, enhances autophagy, and induces metabolic alterations in liver organoid cells that mimic key features of hepatic aging. This approach provides an effective model for studying the molecular mechanisms underlying liver aging.[71]

4.2. Characteristics of aging models of different tissue organoids

Aging is characterized by a series of conserved cellular and molecular alterations that collectively diminish tissue homeostasis and regenerative capacity. Rather than detailing each phenomenon extensively, these core aging features can be summarized concisely as follows. At the cellular level, senescence progressively accumulates, driven by persistent DNA damage signaling, telomere erosion, and chromatin remodeling that culminate in stable cell-cycle arrest and the secretion of pro-inflammatory senescence-associated secretory phenotype (SASP) factors. Mitochondrial dysfunction represents a second major axis, marked by reduced oxidative phosphorylation efficiency, increased reactive oxygen species (ROS) leakage, and impaired metabolic flexibility. Aging also compromises proteostasis through declining autophagy–lysosome activity and an increased protein misfolding. These intracellular changes are accompanied by stem cell exhaustion, reflected in reduced self-renewal, altered lineage commitment, and disruption of niche-derived cues. At the tissue level, aging remodels the ECM, increasing stiffness and altering mechanotransduction pathways that further impair cellular function. Together, these hallmarks provide a streamlined mechanistic framework for interpreting how organoid systems recapitulate age-associated phenotypes while avoiding redundant elaboration of widely known aging biology.[72]

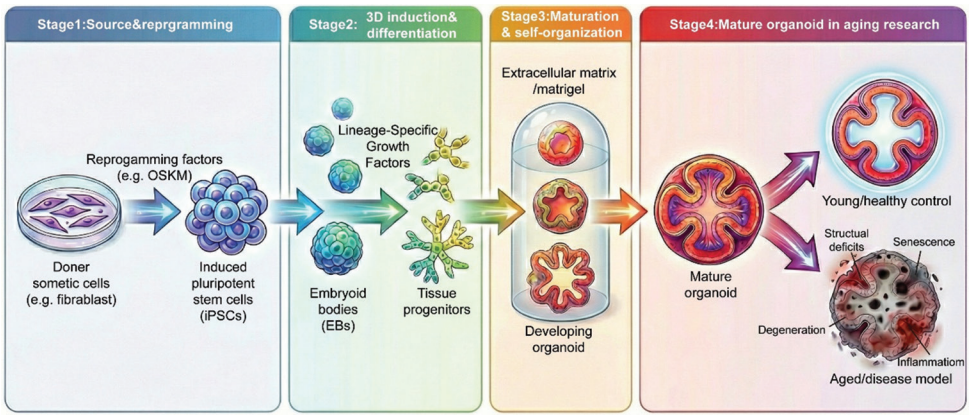

Figure 3. Schematic workflow of human organoid generation and its application in aging mechanism research. The graphical elements were produced with the assistance of the AI tool Gemini, while the overall mechanistic diagram was constructed using Adobe Illustrator.

Cellular composition, structural changes, and functional decline are the three dimensions typically characterized by aging models of different tissue organoids. Taking the brain organoid aging model as an example, the proportion of neural stem cells gradually decreases with the progression of aging, and the ratio of neurons to glial cells also changes.[73] Some of the studies have shown that the number of neurons responsible for the synthesis and transmission of neurotransmitters may decrease, thereby impairing nerve signal transduction.[74-76] Concurrently, at the structural level, the hierarchical organization of brain organoids becomes indistinct, synaptic connections between neurons are diminished, and the degree of nerve fiber myelination is reduced. These changes affect the conduction velocity of nerve impulses. Functional decline is mainly manifested by reduced electrophysiological activity, including decreased frequency and amplitude of electroencephalogram signals, a diminished ability to respond to neurotransmitters, and downregulation of genes related to learning and memory.[77,78] The pathological mechanisms underlying brain functional decline in neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD) are similar, providing important clues for further exploration of disease pathogenesis.[79,80]

Changes in the cellular composition of aging intestinal organoid models are manifested as decreased stemness and proliferative capacity of intestinal stem cells, leading to reduced generation of new cells in the crypts and gradual accumulation of senescent cells. The mucus secretion function of goblet cells may be impaired, thereby compromising intestinal barrier integrity.[44] The ability of Paneth cells to secrete antimicrobial peptides is also reduced, weakening intestinal resistance to pathogens. Structurally, the crypt–villus architecture of intestinal organoids becomes irregular, crypt depth decreases, and villi shorten, impairing digestive and absorptive functions. Functional decline is reflected in a reduced capacity to absorb nutrients such as glucose and amino acids.[81] Contractile activity is reduced, potentially slowing luminal transit-like movement.[17] At the same time, intestinal immune dysfunction may occur, accompanied by increased secretion of inflammatory factors, leading to chronic intestinal inflammation.[21]

In aging liver organoid models, hepatocyte morphology changes, including increased cell volume, nuclear shrinkage, and reduced mitochondrial number and function, leading to abnormal cellular energy metabolism.[82] The activation state of hepatic stellate cells (HSCs) is altered, and excessive activation results in the secretion of large amounts of ECM, conferring a fibrotic tendency to liver organoids.[83] Structurally, the lobular organization of liver organoids becomes disordered, and the intercellular connections between hepatocytes loosen. Functional decline is characterized by diminished hepatic metabolic activity and a concomitant reduction in the capacity to detoxify pharmaceutical agents and toxins, exemplified by a reduced rate of acetaminophen metabolism. In addition, the liver's ability to synthesize proteins and lipids may be impaired, and lipid accumulation may occur, leading to pathological changes associated with liver diseases such as nonalcoholic fatty liver disease.[84]

Although long-term culture and stress-induced senescence remain the most widely used strategies for generating aging organoids, the extent to which these approaches recapitulate natural human aging is increasingly questioned. *In vitro* aging models typically rely on prolonged passaging, oxidative stress exposure, or DNA damage induction to accelerate senescence; however, these perturbations activate only a subset of the molecular events occurring during physiological aging. Natural aging involves a coordinated and gradual interplay of telomere attrition, mitochondrial decline, epigenetic drift, immune dysregulation, ECM remodeling, and systemic metabolic cues—features that are only partially captured by current induction methods.[85-87] For example, oxidative stress models generate robust ROS-driven damage but fail to reproduce the chronic, low-grade inflammatory environment characteristic of inflammaging. Similarly, DNA damage-based protocols induce acute genomic instability but do not mimic the long-term epigenetic remodeling or stem cell exhaustion observed in aged tissues. Even long-term culture, while valuable for observing spontaneous senescence, lacks the vascular perfusion, immune surveillance, and endocrine regulation that shape aging trajectories *in vivo*.[88] Consequently, existing organoid aging models more closely approximate "accelerated stress responses" rather than true organismal aging.

To overcome these limitations, next-generation strategies are emerging that aim to reconstruct the multidimensional nature of human aging within organoid systems. Gene-editing approaches targeting key aging regulators—such as *TERT*, *WRN*, *LMNA*, or mitochondrial maintenance genes—enable the creation of genetically defined aging trajectories that more closely parallel physiological decline.[89-91] Integration with microfluidic organ-on-chip platforms introduces vascular-like perfusion, mechanical cues, and controlled nutrient gradients, allowing organoids to experience aging-relevant biomechanical and metabolic environments. Co-culture with iPSC-derived immune cells provides opportunities to model inflammaging, microglial priming, and immune–epithelial crosstalk, which are absent in traditional organoid systems. Metabolic engineering, including modulation of nicotinamide adenine dinucleotide pathways or mitochondrial biogenesis, offers another avenue to approximate age-associated metabolic collapse. Finally, the

application of DNA methylation-based epigenetic clocks to organoids provides an objective framework for quantifying how closely engineered models approximate natural aging states.[92] Together, these innovations point toward a more comprehensive and physiologically relevant organoid aging paradigm, bridging the gap between artificial induction and true biological aging.

4.3. Model validation and evaluation indicators

The validation and evaluation of organoid aging models require the comprehensive application of multiple methods, including analyses of cell morphology, gene expression, and function. Observation of cell morphology is an important approach for the visual evaluation of organoid aging. Microscopic analysis of senescent organoid cells reveals several hallmark features, including increased cell volume, irregular shape, enlarged nuclei and cytoplasm, and dense chromatin. In established neural organoid aging models, there is a demonstrable loss of neuronal axons and dendrites, as well as a reduction in branch number.[49] With the aid of electron microscopy, organelle alterations can be more clearly visualized: mitochondria in senescent cells appear swollen,[93] cristae structures become blurred, and the endoplasmic reticulum is dilated or ruptured. These morphological changes provide initial visual evidence for validating organoid aging models.

A key approach for validating aging models is the analysis of gene expression. Changes in the expression of aging-related genes can be detected using real-time quantitative polymerase chain reaction, gene chips, or RNA sequencing (RNA-Seq). Cell cycle regulatory genes such as *p16* and *p21* are significantly upregulated in senescent organoids; these genes induce cell cycle arrest in the G1 phase by inhibiting cyclin-dependent kinase (CDKs) activity,[94] thereby initiating cellular senescence. In addition, downregulation of telomerase reverse transcriptase (TERT) leads to telomere shortening, which is known to accelerate cellular senescence.[89] Detection of the expression levels of such key genes enables comprehensive evaluation of aging status, characterization of aging-related features, and analysis of associated molecular interaction mechanisms in organoid models.

Functional testing constitutes another critical component in the evaluation of organoid aging models, and the specific assays vary depending on tissue type. In brain organoid research, functional status can be evaluated by measuring electrophysiological activity. Multi-electrode array technology is commonly used to record electroencephalogram signals of brain organoids and to analyze changes in signal frequency, amplitude, and synchrony.[95] Functional decline in aging brain organoids is typically manifested by decreased frequency, reduced amplitude, and impaired synchronization of electrical activity. Similarly, aging in intestinal organoids can be assessed by examining nutrient absorption capacity, such as the efficiency of glucose or amino acid uptake and transport using radiolabeled substrates.[44] In liver organoid models, retention of detoxification capacity can be evaluated by measuring the activity of drug-metabolizing enzymes. For example, reduced activity of the cytochrome P450 enzyme system in aged liver organoids leads to reduced metabolism of drugs and toxins, reflecting functional hepatic decline.[96] Through the integrated application of these validation and evaluation indicators, the validity and reliability of organoid aging models can be accurately assessed, providing a robust experimental foundation for aging research.

5. Organoid-based deciphering of cellular and tissue aging mechanisms

5.1. Organoid-unveiled mechanisms of cellular senescence

Cellular senescence is a stable and irreversible state of cell cycle arrest triggered by intrinsic (such as replication exhaustion) or extrinsic (such as oxidative stress) stimuli and is characterized by distinct phenotypic markers, including morphological alterations, decreased proliferation capacity, increased SA-β-gal activity, and secretion of SASP.[97] As shown in Figure 4, owing to their ability to replicate *in vivo*-like cell–cell interactions and microenvironmental signals, organoids have become powerful models for dissecting three evolutionarily conserved pathways that drive cellular aging.

5.1.1. Cell cycle dysregulation: A central trigger of senescence

The eukaryotic cell cycle is a finely regulated process governed by a regulatory network composed of cell cycle proteins, CDKs, and CDK inhibitors (CKIs), encompassing key stages such as interphase (G1 and G2), DNA synthesis (S phase), and mitosis (M phase).[98] As recapitulated in senescent organoids, disruption of this regulatory network constitutes a major trigger for initiating cell cycle arrest and driving cellular senescence.

Organoid technology provides a powerful means to directly observe age-associated perturbations in cell cycle regulators. Taking long-term cultured intestinal organoids (an epithelial cell senescence model) as an example, the expression levels of the G1→S phase-promoting cyclin D1 and E decrease synchronously as cells gradually acquire senescent characteristics.[99] These two cyclins form active complexes with CDK4/6 and CDK2, respectively, which phosphorylate retinoblastoma protein, a key mechanism enabling cell exit from G1 phase and entry into S phase. In senescent intestinal organoids, downregulation of

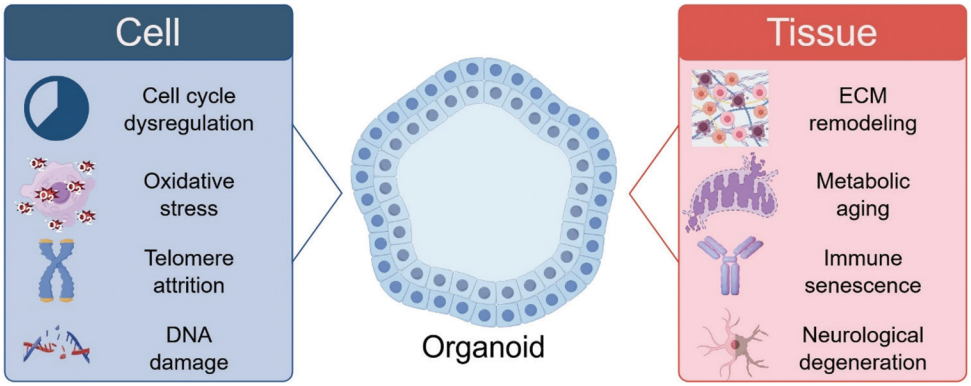

Figure 4. Key directions in aging research using organoids at the cellular and tissue levels. Created with Figdraw 2.0.

cyclins D1 and E directly inhibits CDK4/6 and CDK2 kinase activity, thereby blocking cell cycle progression at the G1/S checkpoint.

At the same time, CKIs, particularly p16INK4a (CDKN2A) and p21Cip1 (CDKN1A), are significantly upregulated in senescent organoids. p16INK4a inhibits CDK4/6 activity by specifically binding to CDK4/6 and preventing its association with cyclin D1, thereby blocking retinoblastoma protein phosphorylation. In contrast, p21Cip1 exerts a broad-spectrum inhibitory effect by forming complexes with multiple CDK–cyclin combinations, such as CDK2–cyclin E, CDK2–cyclin A, and CDK1–cyclin B, leading to coordinated cell cycle arrest at both the G1 and G2 phases. This CKI-mediated arrest exhibits tissue specificity: in brain organoids, increased expression of p16INK4a and p21Cip1 is closely associated with decreased proliferation and impaired neurogenesis of neural stem/progenitor cells, which is highly consistent with the progressive loss of neural regenerative capacity observed during brain aging *in vivo*.[100,101]

Collectively, these findings confirm that dysregulation of the cell-cycle regulatory machinery is a conserved driver of cellular aging and that organoids provide a physiologically relevant platform for resolving the spatiotemporal dynamics of this process, including tissue-specific differences in regulator expression.

5.1.2. Oxidative stress: A multifaceted driver of senescence

Significant accumulation of ROS is a hallmark of aging organoids subjected to long-term culture or oxidative stress-inducing conditions. Excessive ROS accumulation is primarily attributed to impairments in mitochondrial respiratory chain function. Defects in the mitochondrial electron transport chain, such as reduced activity of complexes I/III, lead to electron transport leakage and ROS overproduction. This process is further exacerbated by downregulation of key antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase in aging organoids, creating a feedforward loop that amplifies oxidative damage.[102] Excess ROS can irreversibly damage critical cellular macromolecules, and organoid studies have revealed the specificity of these effects:

(i) Proteins – ROS-mediated oxidation of amino acid residues (e.g., cysteine, methionine) results in the formation of carbonylated proteins that lose structural integrity and functional activity, thereby disrupting signaling cascades and metabolic pathways.[103]
(ii) Lipids – ROS triggers lipid peroxidation of membrane phospholipids, disrupting membrane fluidity and permeability and generating toxic byproducts (e.g., malondialdehyde) that further propagate oxidative stress.[104]
(iii) DNA–ROS causes single-strand breaks, double-strand breaks, and base modifications (e.g., 8-oxoguanine), thereby activating the DNA damage response pathway.[105]

5.1.3. Telomere attrition: The "clock" of senescence

Telomeres are specialized nuclear protein structures located at the extremities of eukaryotic chromosomes. They are constituted of hexanucleotide repeats (TTAGGG in humans) and associated protective complexes (such as telomeric repeat binding factor [TRF] 1, TRF2, and TIN2). Their primary function is to protect chromosome termini from fusion, degradation, and aberrant activation of the DNA damage response. The "telomere clock" hypothesis posits that telomeres progressively shorten with each cell division due to the end-replication defects in DNA polymerase, and that cells enter senescence or apoptosis once telomeres reach a critical length.[106] By preserving the replicative capacity of cells across multiple passages, organoid technology has allowed scientists to track telomere dynamics and their roles in aging over time.

In organoids derived from somatic tissues such as skin and liver, telomere length gradually decreases with increasing culture passages. Early-passage organoids maintain relatively stable telomere length; however, telomeric repeats

are progressively lost as cells undergo repeated division.[19,107] Upon reaching a critical length, telomeres induce a senescent cellular phenotype, manifesting in increased cell size, abnormal morphology, elevated SA-β-gal activity, and reduced clonogenic capacity. In skin organoids, which serve as a model of epithelial aging, telomere shortening correlates with reduced proliferation of basal keratinocytes and impaired tissue stratification. These features effectively recapitulate key aspects of physiological skin aging.

Telomerase is a ribonucleoprotein complex consisting of a catalytic subunit (TERT) and an RNA template (telomerase RNA component) that counteracts telomere shortening by adding telomeric repeats to chromosome ends. In most somatic cells, telomerase activity is repressed, leading to replicative senescence.[108] In contrast, telomerase remains active in stem cells, germ cells, and cancer cells to maintain telomere length. Recent organoid-based studies have further elucidated the relationship between telomerase dysfunction and aging. A cardiac organoid model demonstrated that telomere shortening results in aberrant activation of the transcription factor FO forkhead box C1 due to disruption of the 3D chromatin architecture, specifically reduced topologically associating domain insulation. This process triggers mitochondrial respiratory dysfunction and dysregulation of cardiomyocyte contraction, thus recapitulating telomere shortening-driven cardiac aging phenotype *in vitro* for the first time.[109] Notably, these effects are difficult to reproduce in conventional 2D culture systems.

5.2. Organoid-based elucidation of tissue aging molecular mechanisms

Tissue aging is a progressive and systemic process driven by the cumulative dysfunction of individual cells, coupled with dysregulated intercellular communication, ECM remodeling, and aberrant signaling network activity.[110] As shown in Figure 4, organoids recapitulate tissue-specific architecture and cell–cell interactions, thereby providing a unique platform to study how molecular changes coordinate to drive tissue-level decline. The following discussion focuses on key mechanisms of tissue aging revealed through organoid research, with particular emphasis on the brain, which is widely regarded as a paradigm for age-related neurodegenerative disorders.

5.2.1. Signaling pathway dysregulation in tissue aging

Cell signaling pathways regulate fundamental physiological processes such as cell fate determination, metabolic activity, and tissue repair. Several representative signaling pathways relevant to organoid aging research are summarized in Table 1. Dysregulation of these pathways in aging organoids is similar to age-associated pathological changes observed *in vivo*, underscoring their critical roles as drivers of tissue decline. Using organoid models, researchers have successfully identified tissue-specific signaling defects, particularly in the brain, a region profoundly affected by aging and closely associated with neurodegenerative diseases such as AD and PD.[111,112]

5.2.2. Age-associated gene expression remodeling in tissues

Transcriptome sequencing (RNA-seq) of aging organoids has enabled the systematic profiling of gene expression changes, allowing identification of key regulatory genes whose dysregulation links cellular senescence to tissue-level aging. Organoid models facilitate the discovery of both tissue-specific gene expression signatures and conserved aging-associated genes through comparisons between young and senescent organoids derived from the same tissue or patient.[118] These age-related gene expression changes cluster into distinct functional categories as follows:

(i) Cell cycle- and senescence-associated genes: Consistent with established mechanisms of cellular senescence, senescent brain organoids exhibit significant upregulation of cell cycle inhibitors (p16INK4a, p21Cip1) and senescence markers.[119] Elevated p16INK4a expression in neural stem cells inhibits CDK4/6 activity, blocking cell cycle progression and reducing neurogenesis, thereby disrupting the cellular composition and functional integrity of brain organoids.[49] This upregulation is conserved across organoid types, including liver and skin organoids, highlighting a universal role for these genes in tissue aging.[84,107]

(ii) Neuronal function-related genes: Aging brain organoids display downregulation of genes critical for neurotransmitter synthesis, transport, and synaptic function—tissue-specific changes that underlie neural functional decline.

- Dopaminergic signaling – Tyrosine hydroxylase, the rate-limiting enzyme in dopamine synthesis, and the dopamine transporter (SLC6A3) are reduced in PD patient-derived brain organoids, leading to decreased dopamine levels and impaired dopaminergic signaling, closely mirroring *in vivo* PD pathology.[120]
- Cholinergic signaling – Choline acetyltransferase, which catalyzes acetylcholine synthesis, is downregulated in AD-associated brain organoids, correlating with reduced acetylcholine levels and impaired cholinergic signaling, consistent with the learning and memory impairments observed in AD patients.[121]

Table 1. Representative signaling pathways involved in organoid aging research

Signaling pathway	Physiological function in organoids	Dysregulation in senescent organoids	Functional consequences for tissue aging
Wnt/β-Catenin	Mediates neural stem cell (NSC) proliferation, differentiation, and neural precursor migration; maintains intestinal crypt homeostasis	Aberrant overactivation in AD-associated brain organoids, driven by reduced secretion of Wnt antagonists (e.g., DKK1) and increased nuclear translocation of β-catenin[113]	Excessive NSC proliferation, unbalanced neurogenesis, and formation of morphologically/functionally abnormal neurons (e.g., reduced dendritic arborization, defective synaptic connectivity). This dysregulation is linked to β-amyloid plaque accumulation and tau hyperphosphorylation, accelerating neuronal loss and cognitive-like dysfunction—phenotypes recapitulated in AD patient-derived brain organoids
Notch	Regulates NSC self-renewal and lineage commitment via juxtacrine signaling; maintains the NSC pool in brain organoids[114]	Progressive downregulation of Notch ligands (e.g., Jagged1) and receptors (e.g., Notch1) in senescent brain organoids[115], leading to reduced cleavage of the Notch intracellular domain and impaired downstream target gene expression	Diminished NSC self-renewal capacity, premature differentiation, and depletion of the NSC pool. This reduces the production of neurons and glial cells, impairs tissue repair, and mimics neurodegenerative phenotypes of age-related dementias—effects that are reversible by Notch pathway activation in organoids[116]
mTOR	Acts as a central nutrient/energy sensor; regulates cell growth, protein synthesis, autophagy, and mitochondrial metabolism in organoids	Constitutive overactivation in senescent brain/liver organoids, driven by dysregulated nutrient sensing (e.g., reduced AMPK activity) and increased mTORC1 complex formation	Promotes excessive cell growth, metabolic reprogramming, and ROS overproduction while inhibiting autophagy, leading to accumulation of misfolded proteins (e.g., α-synuclein in PD patient-derived organoids) and damaged organelles. This exacerbates mitochondrial dysfunction and neuronal senescence, contributing to tissue functional decline—effects that are attenuated by mTOR inhibitors in organoid models[117]

Abbreviations: AD: Alzheimer's disease; AMPK: Adenosine 5'-monophosphate-activated protein kinase; DKK1: Dickkopf 1; mTOR: Mechanistic target of rapamycin; mTORC1: Mechanistic target of rapamycin complex 1; PD: Parkinson's disease; ROS: Reactive oxygen species

6. Applications of organoids in aging-related disease research

6.1. Neurodegenerative diseases

In recent years, organoid-based neurodegeneration research has substantially expanded understanding of AD and PD, revealing mechanistic layers that extend beyond classical linear models of protein aggregation and neuronal loss. Unlike 2D cultures or animal models, human brain and midbrain organoids reproduce key aspects of human neural development, cytoarchitecture, and lineage diversification, thereby enabling the emergence of cellular interactions and temporal signaling trajectories that are fundamentally human-specific.[122] In AD organoids, longitudinal profiling reveals that disruptions in WNT–GSK3β signaling, synaptic maturation pathways, and metabolic regulation arise well before detectable β-amyloid (Aβ) deposition, indicating that early pathogenic events are closely linked to human cortical differentiation. These developmental perturbations coincide with dynamic changes in γ-secretase subunit composition that shift the Aβ42/Aβ40 ratio during early corticogenesis—an observation not captured in murine models and one that provides a plausible mechanism for the initial onset of Aβ dyshomeostasis.[123] Moreover, the spontaneous generation of astrocytes and microglia-like cells in long-term organoid cultures allows the identification of multicellular pathogenic circuits, including altered neuron–astrocyte metabolic coupling and triggering receptor expressed on myeloid cells 2–apolipoprotein E-associated microglial activation states that amplify synaptic vulnerability through non-cell-autonomous inflammatory loops.[124] Together, these findings indicate that AD arises from complex disruptions of human-specific cellular communication networks rather than from isolated protein accumulation alone.

6.1.1. AD

As summarized in Table 2, the translational relevance of organoid research has become increasingly evident. AD is a common neurodegenerative disorder characterized by extracellular plaques formed by Aβ aggregation, intracellular neurofibrillary tangles caused by abnormal tau phosphorylation, neuronal loss, and synaptic dysfunction. With the rapid aging of the global population, the incidence of AD is increasing annually, imposing a substantial burden on both society and families.[126] As an emerging research tool, brain organoids provide a new perspective for exploring the pathogenesis of AD.[113]

A series of significant advances has been achieved through the application of brain organoids to the study of AD pathogenesis. Accumulation of Aβ in brain organoids has been shown to initiate a cascade of pathological alterations. Elevated Aβ levels induce inflammatory responses that activate microglia and astrocytes, which subsequently release pro-inflammatory factors, including

Table 2. Neurodegenerative diseases modeled using organoids

Neurodegenerative disease	Key pathologies modeled	Key cellular/molecular pathways implicated	Limitations of current models
Alzheimer's disease	Aβ plaques; tau tangles; synaptic loss; neuroinflammation	APP/PSEN1 processing defects; tau hyperphosphorylation; TREM2–APOE signaling dysfunction; mitochondrial impairment[111]	Immature neural networks; lack of vasculature; limited microglial functionality; restricted long-range connectivity
Parkinson's disease	α-synuclein aggregation; dopaminergic neuron loss; mitochondrial dysfunction	PINK1/Parkin mitophagy defects; LRRK2/GBA1-associated lysosomal impairment; dysfunctional dopamine synthesis and uptake[98]	Immature dopaminergic phenotype; absence of systemic or gut–brain axis signals; poor neuromelanin formation
Amyotrophic lateral sclerosis	Motor neuron degeneration; TDP-43 aggregation; NMJ impairment	RNA-binding protein dysregulation; cytoskeletal and axonal transport defects; glutamate excitotoxicity[125]	Limited NMJ maturation; absence of corticospinal projection physiology; high iPSC line variability
Frontotemporal dementia	Cortical neuron loss; Tau/TDP-43 pathology; dendritic atrophy	MAPT mutation-associated effects; GRN/C9orf72-linked lysosomal dysfunction; synaptic network disruption[86]	Incomplete cortical regionalization; insufficient glial and vascular components; requirement for long-term culture

Abbreviations: APOE: Apolipoprotein E; APP: Amyloid-beta precursor protein; GBA1: β-glucosylceramidase; GRN: Granulin precursor; iPSC: Induced pluripotent stem cell; LRRK2: Leucine-rich repeat kinase 2; MAPT: Microtubule-associated protein tau; NMJ: Neuromuscular junction; PINK1: PTEN-induced kinase 1; PSEN1: Presenilin protein 1; TDP-43: Transactive response DNA binding protein of 43 kDa; TREM2: Triggering receptor expressed on myeloid cells 2.

tumor necrosis factor-α (TNF-α) and interleukin (IL) 1β, thereby exacerbating neuronal damage. In addition, Aβ aggregation induces mitochondrial dysfunction, disrupts energy metabolism, increases neuronal susceptibility to oxidative stress, and accelerates neuronal death.[127] Regarding tau pathology, brain organoid studies have shown that Aβ aggregation promotes tau hyperphosphorylation through activation of kinases such as GSK-3β.[128] Hyperphosphorylated tau dissociates from microtubules, forms neurofibrillary tangles, disrupts neuronal cytoskeletal integrity, impairs neuronal function, and ultimately blocks neural signal transmission.[129]

Brain organoids also hold substantial potential for drug screening and therapeutic target validation in AD research. The generation of brain organoid models carrying AD-related gene mutations (e.g., *APP* and *PSEN1*) enables faithful recapitulation of patient-specific pathological features. These models can be used to screen compounds that inhibit Aβ aggregation, reduce tau phosphorylation, or protect neuronal viability.[130,131] As illustrated in Figure 5, brain organoid models have been applied to evaluate a variety of candidate therapeutic agents. Certain small-molecule compounds suppress Aβ production and aggregation by modulating γ-secretase activity, thereby reducing Aβ-induced neurotoxicity in brain organoid models. In addition, inhibitors targeting GSK-3β effectively reduce tau phosphorylation and improve neuronal function.[132] Brain organoids can further be used to validate therapeutic targets through gene editing approaches, such as gene knockout or overexpression, followed by assessment of their effects on AD-related pathology. For example, overexpression of neuroprotective genes such as *BDNF* enhances neuronal survival and mitigates neuronal damage induced by aberrant Aβ and tau pathology.[133]

6.1.2. PD

PD is another prevalent neurodegenerative disorder, mainly characterized by the progressive loss of dopaminergic neurons in the substantia nigra of the midbrain, leading to motor symptoms such as bradykinesia, tremor, and muscular rigidity. Aging is one of the major risk factors for PD, and disease prevalence increases significantly with advancing age. Human brain organoid models provide a powerful tool for elucidating PD pathogenesis.[134]

The application of human brain organoid models has enabled deeper insight into mechanisms underlying astrocyte dysfunction, aberrant glycosylation, and protein aggregation in PD. Researchers at the New York Stem Cell Institute demonstrated, using a human brain mesencephaloid model, that astrocytes play a pivotal role in PD pathogenesis. In the absence of the DJ1 protein, which is associated with PD, astrocytic protein homeostasis becomes disrupted, leading to lysosomal dysfunction, increased aggregation of pathogenic α-synuclein, and subsequent neuronal death. These findings indicate that astrocyte dysfunction, abnormal glycosylation, and extensive protein aggregation are central features of DJ1-related familial PD.[135]

Glycosylation is a ubiquitous biochemical modification in living organisms, and excessive accumulation of advanced glycation end products (AGEs) can impair cellular function. Elevated levels of AGEs have been detected in both PD patient brain tissue and human brain organoid models. Accumulation of AGEs disrupts protein

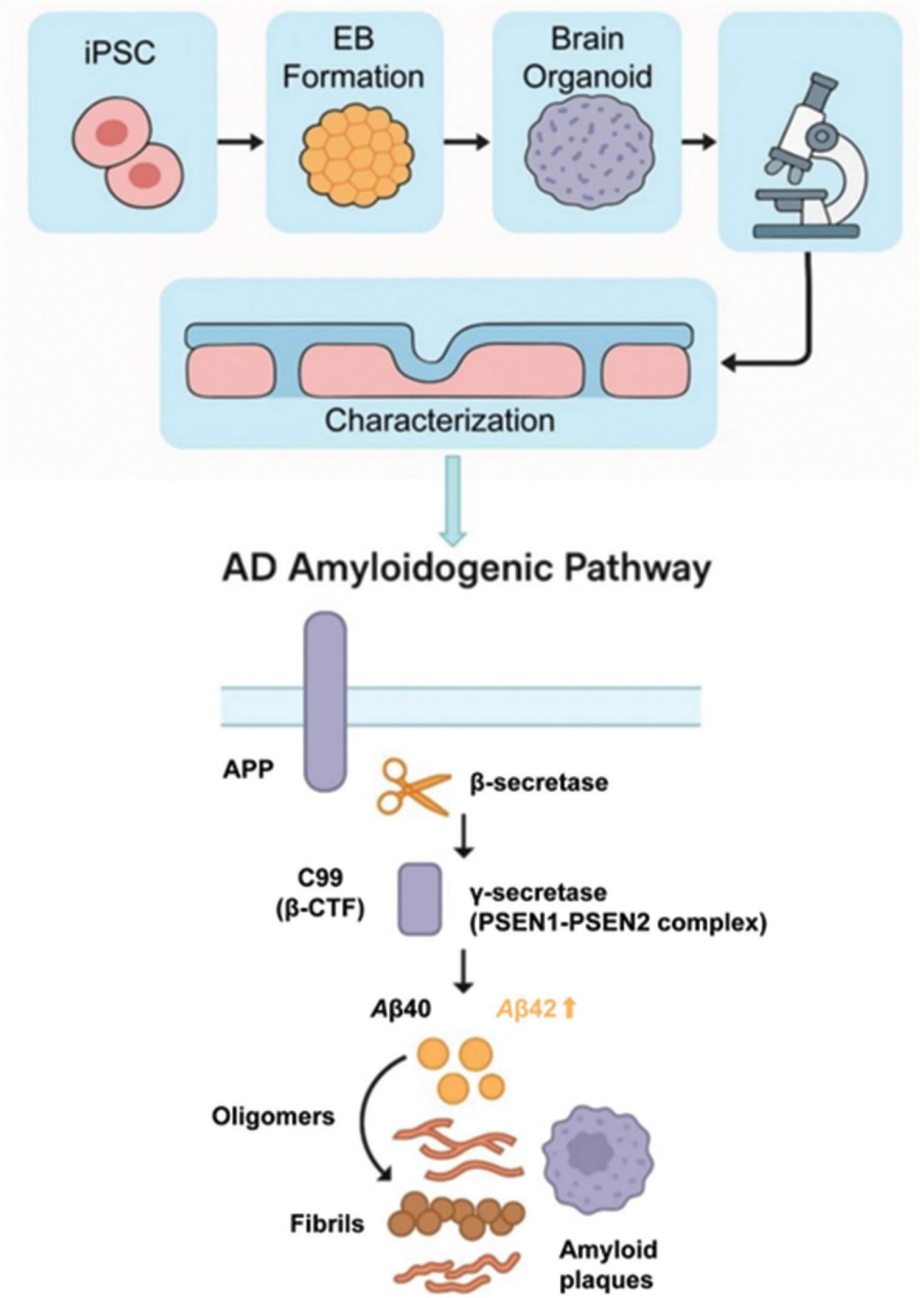

Figure 5. Schematic representation of brain organoids applied in aging research, using Alzheimer's disease as an example. The graphical elements were produced with the assistance of the AI tool Gemini, while the overall mechanistic diagram was constructed using Adobe Illustrator.
Abbreviations: Aβ: β-amyloid; APP: Amyloid-beta precursor protein; PSEN: Presenilin protein; β-CTF: beta-carboxyl-terminal fragment

quality control mechanisms, thereby compromising neuronal survival. Notably, levels of methylglyoxal-derived hydroxyimidazolone, an advanced glycosylation modification product, were significantly increased in DJ1-deficient human brain organoids, suggesting exacerbated glycosylation-associated damage.[136] Furthermore, AGEs may affect the abundance and phosphorylation status of α-synuclein, thus playing an important role in PD pathogenesis.

6.2. Cardiovascular diseases

Cardiovascular disease is a major cause of mortality worldwide. The etiology of this condition is multifactorial and closely related to the aging process. As demonstrated in Table 3, cardiac organoids are an emerging research tool with significant potential applications in the study of cardiovascular diseases, including myocardial cell aging and cardiac fibrosis. Furthermore, cardiac organoids

Table 3. Applications of organoids in aging-related disease research

Disease category	Specific disease	Organoid application	Key research advances
Cardiovascular	Myocardial senescence	Mechanistic study of mitochondrial dysfunction and oxidative stress	Heart organoids demonstrate an age-related decline in mitochondrial membrane potential and SOD/CAT activity. Activation of the p53–p21 and mTOR pathways correlates with impaired cardiomyocyte proliferation[159]
	Cardiac fibrosis	Pathogenesis modeling and personalized drug screening	Organoids show TNF-α/IL-6-induced fibroblast activation and collagen deposition. Angiotensin II-induced fibrosis is mitigated by ACE inhibitors in patient-derived organoids[142]
Metabolic	Diabetes (liver-related)	Insulin resistance and gluconeogenesis mechanism study	Liver organoids from aged donors exhibit defects in IRS phosphorylation and increased PEPCK/G6Pase activity. Mitochondrial dysfunction and oxidative stress exacerbate hyperglycemia[151]
	Diabetes (islet-related)	β-cell dysfunction and inflammation mechanism study	Pancreatic islet organoids show reduced glucose-stimulated insulin secretion and IL-1β/TNF-α-mediated β-cell apoptosis. Calcium homeostasis imbalance and mitochondrial damage are observed[154]
	Non-alcoholic fatty liver disease (NAFLD)	Lipid metabolism and ER stress mechanism study	Senescent liver organoids exhibit increased FATP/FAS expression and reduced β-oxidation enzyme levels. ER stress-induced UPR activation promotes lipid accumulation[158]
Oncology	Pancreatic cancer	Chemotherapy response prediction and personalized medicine	Patient-derived organoids accurately predict chemotherapy efficacy, with gene signatures correlating with drug sensitivity[160]
	Neuroblastoma	Immunotherapy evaluation and drug resistance study	Neuroblastoma organoids co-cultured with PBMCs demonstrate dinutuximab-induced ADCC activity. Luciferase reporter systems enable real-time cytotoxicity monitoring[161]
Liver diseases	Cirrhosis and fibrosis	Pathogenesis modeling and antifibrotic drug development	ARPKD-mutant hepatic organoids recapitulate bile duct abnormalities and collagen deposition. TGF-β pathway activation in cholangiocytes drives myofibroblast differentiation[35,162]
Gastrointestinal	Crohn's disease	T-cell-mediated epithelial injury mechanism study	Autologous organoid–T cell co-cultures reveal CD103/NKG2D-dependent epithelial cell death in Crohn's disease. Blocking antibodies mitigate inflammatory damage[163]
Renal diseases	Drug-induced nephrotoxicity	Multisegmented nephrotoxicity assessment and biomarker discovery	Kidney organoids express functional OAT/OCT transporters. Cisplatin-induced proximal tubular injury is rescued by cimetidine, while puromycin selectively damages podocytes[164]
Ophthalmology	Glaucoma	Retinal ganglion cell death mechanism and neuroprotective drug development	Retinal organoids derived from glaucoma patients show RGC apoptosis and mitochondrial dysfunction. ATP/ADP biosensors enable high-throughput drug screening[165]
Orthopedics	Osteonecrosis of the femoral head	Vascularized bone[166,167] regeneration and biomaterial optimization[168,169]	Engineered ECM–DNA–CPO hydrogels support synchronous angiogenesis and mineralization in bone organoids[170]. *In vivo* transplantation demonstrates enhanced osteointegration[171]

Abbreviations: ACE: Angiotensin-converting enzyme; ADCC: Antibody-dependent cell-mediated cytotoxicity; ARPKD: Autosomal recessive polycystic kidney disease; CAT: Catalase; CD103: Cluster of differentiation 103; CPO: Calcium phosphate oligomer; ECM: Extracellular matrix; ER: Endoplasmic reticulum; FAS: Fatty acid synthase; FATP: Fatty acid transporter; G6Pase: Glucose 6-phosphatase; IL: Interleukin; IRS: Insulin receptor substrate; mTOR: Mechanistic target of rapamycin; NKG2D: Natural killer group 2D ligand; OAT: Organic anion transporter; OCT: Organic cation transporter; PBMCs: Peripheral blood mononuclear cells; PEPCK: Phosphoenolpyruvate carboxykinase; RGC: Retinal ganglion cell; SOD: Superoxide dismutase; TGF-β: Transforming growth factor-beta; TNF-α: Tumor necrosis factor-α; UPR: Unfolded protein response.

hold considerable promise for drug development and personalized treatment.[137]

In the field of cardiomyocyte aging, cardiac organoids provide a powerful platform for an in-depth understanding of age-related changes in cardiomyocytes. With aging, a series of structural and functional changes occur in cardiomyocytes, such as increased cell size, mitochondrial dysfunction, and elevated oxidative stress levels.[138] Investigations using cardiac organoids have revealed substantial alterations in mitochondrial morphology and function in aged cardiomyocytes. Declines in mitochondrial membrane potential and abnormal energy metabolism result in reduced myocardial contractility. Aging has also been demonstrated to decrease the activity of antioxidant enzymes, such as superoxide dismutase and catalase, resulting in the accumulation of ROS in cells and further damage to cardiomyocytes. Research has identified that aging-related pathways, including the p53–p21 and mTOR

signaling pathways, exhibit aberrant activation or inhibition in cardiac organoids. These alterations have been shown to affect key cellular processes, such as cardiomyocyte proliferation, differentiation, and survival.[139,140]

Cardiac fibrosis is a significant pathological process in cardiovascular diseases, and cardiac organoid models play a pivotal role in studying its pathogenesis. Cardiac fibrosis is defined as the abnormal deposition of ECM in myocardial tissue, leading to impaired cardiac structure and function. In cardiac organoid models, several factors have been identified as triggers for cardiac fibrosis, including inflammatory mediators and angiotensin II. Inflammatory factors such as TNF-α and IL-6 have been shown to activate cardiac fibroblasts, resulting in their proliferation and the secretion of large amounts of ECM components, including collagen and fibronectin. This process contributes to myocardial scarring and fibrosis.[141] Angiotensin II promotes fibroblast activation and proliferation while inhibiting apoptosis through receptor-mediated activation of downstream signaling pathways, thereby exacerbating cardiac fibrosis.[142] In addition, studies have shown that fibroblast function is altered in aging cardiac organoids, with increased sensitivity to profibrotic signals, further driving the progression of cardiac fibrosis.[143]

Cardiac organoids also have substantial potential in drug development and personalized therapy. By constructing disease models such as myocardial infarction and heart failure, these organoids can serve as platforms for the screening and evaluation of cardiovascular drugs.[144] Research using cardiac organoid models has demonstrated that certain drugs can improve cardiomyocyte function and reduce cardiac fibrosis. For example, calcium channel blockers regulate calcium homeostasis in cardiomyocytes and improve myocardial contractile function, while angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers inhibit angiotensin II signaling and reduce the risk of cardiac fibrosis. Because cardiac organoids can be derived from patient-specific cells, personalized drug screening and treatment strategies can be achieved.[145] Testing drugs on autologous cardiac organoids allows prediction of individual patient responses, providing more accurate guidance for clinical treatment and improving therapeutic efficacy and safety.[146]

6.3. Metabolic diseases

Metabolic diseases such as diabetes and fatty liver disease are closely related to aging and seriously affect human health. Liver and islet organoids play an important role in studying the relationship between these metabolic diseases and aging, providing new ideas and methods for elucidating disease pathogenesis and developing prevention and treatment strategies.[147,148]

Liver organoid models play a key role in studying the relationship between diabetes and aging. As an important organ regulating blood glucose, the liver plays a central role in the occurrence and development of diabetes. With aging, hepatic metabolic function gradually declines and insulin resistance increases, leading to imbalances in blood glucose regulation.[149] Studies using liver organoid models have shown that insulin signaling pathways are impaired in aging liver organoids. Specifically, the phosphorylation level of insulin receptor substrate is decreased, thereby blocking activation of the downstream phosphatidylinositol-3 kinase–Akt signaling pathway, and inhibiting hepatic glucose uptake and utilization.[150] Aging also increases the expression and activity of key hepatic gluconeogenic enzymes, such as phosphoenolpyruvate carboxykinase and glucose-6-phosphatase, resulting in increased hepatic glucose output and further aggravation of hyperglycemia. Studies have further demonstrated that impaired mitochondrial function and increased oxidative stress in aging liver organoids trigger hepatocyte injury and inflammatory responses, which exacerbate insulin resistance and dysregulated glucose metabolism.[151]

Islet organoid models are of great value in the study of the pathogenesis and treatment of diabetes. As the primary source of insulin secretion, β-cell dysfunction and reduced β-cell mass are core factors in the onset and progression of diabetes. With aging, the function of pancreatic islet β cells gradually declines, leading to decreased insulin secretion and impaired blood glucose regulation.[152] Studies using islet organoids have shown that insulin secretion by β cells in aging islet organoids is impaired and that their responsiveness to glucose stimulation is diminished. This impairment may be associated with disruptions in β-cell calcium homeostasis, mitochondrial dysfunction, and age-related changes in the expression of genes involved in insulin synthesis and secretion.[153] Moreover, studies have found that increased expression of inflammatory factors, such as IL-1β and TNF-α, in aging islet organoids can damage β cells and further inhibit insulin secretion.[154]

Liver organoid models also provide valuable insights into fatty liver disease by enabling mechanistic studies and the development of prevention and treatment strategies. Fatty liver disease refers to a pathological condition characterized by excessive fat accumulation in the liver and is closely related to factors such as aging, obesity, and metabolic syndrome.[155] In liver organoid models, researchers have documented that aged liver organoids are more prone to lipid accumulation, which is associated with aging-induced dysregulation of hepatic lipid metabolism.[156] Fatty acid uptake and the expression of fatty acid transporters are increased in aged liver organoids, promoting enhanced fatty acid influx into hepatocytes. In addition, the expression and activity of fatty acid synthase are elevated in the liver,

while the expression and activity of enzymes involved in fatty acid β-oxidation are reduced. This imbalance results in increased fatty acid synthesis, decreased lipid oxidation, and ultimately excessive hepatic lipid accumulation.[157] Studies have further shown that endoplasmic reticulum stress is aggravated in aging liver organoids, leading to activation of the unfolded protein response, which disrupts lipid metabolism and cellular function and accelerates the progression of fatty liver disease.[158] Investigations using liver organoids therefore provide a theoretical foundation for the development of therapeutic agents and preventive strategies, including the regulation of lipid metabolism-related genes and the alleviation of endoplasmic reticulum stress.

7. Progress in the combination of organoids with other technologies in aging research

7.1. Organoids and single-cell sequencing technology

Single-cell sequencing technology enables high-throughput analysis of the genome, the transcriptome, and the epigenome at the single-cell level. The integration of this technology with organoid systems has the potential to provide a novel perspective on aging research, facilitating the elucidation of cellular heterogeneity and molecular mechanisms during the aging process with single-cell precision.[118]

In organoid aging models, there are significant disparities in the behavior of different cell types during the aging process. As shown in Figure 6, single-cell sequencing technology enables precise transcriptomic analysis of diverse cell types within organoids, thereby revealing patterns of gene expression changes. Application of single-cell transcriptomic sequencing technology has allowed the identification of significant differences in gene expression profiles among various cell types, including hepatocytes, cholangiocytes, and HSCs, during aging in liver organoids.[172] The expression of metabolism-related genes in hepatocytes shows a downward trend; for example, the expression of key enzymes involved in fatty acid β-oxidation and gluconeogenesis is reduced, resulting in a decline in hepatic metabolic function. In addition, altered expression of genes associated with bile secretion and transport in cholangiocytes affects normal bile excretion.[173]

Imbalances in the expression of genes related to ECM synthesis and degradation in HSCs lead to excessive ECM deposition and the development of liver fibrosis.[174] These findings suggest that single-cell sequencing technology can reveal cell-type-specific molecular changes during aging, thereby providing detailed insights into the mechanisms of liver aging. Furthermore, this technique can be used to study changes in cell–cell interactions within organoids during aging. Cellular communication is essential for the maintenance of normal tissue function, yet these interactions are often disrupted with advancing age. Single-cell sequencing can be employed to analyze changes in the expression of ligand–receptor pairs between different cell types, allowing inference that intercellular communication networks are remodeled.

In brain organoid aging models, single-cell sequencing analyses have revealed a gradual disorganization of communication between neurons and glial cells as aging progresses. Concurrently, neuronal secretion of neurotrophic factors declines, and the neuroprotective functions of glial cells are diminished.[175] This cascade may further accelerate neuronal loss during aging and ultimately contribute to age-related declines in brain function.[176] The integration of single-cell sequencing technology and organoid technology thus facilitates comprehensive exploration of cellular heterogeneity, gene

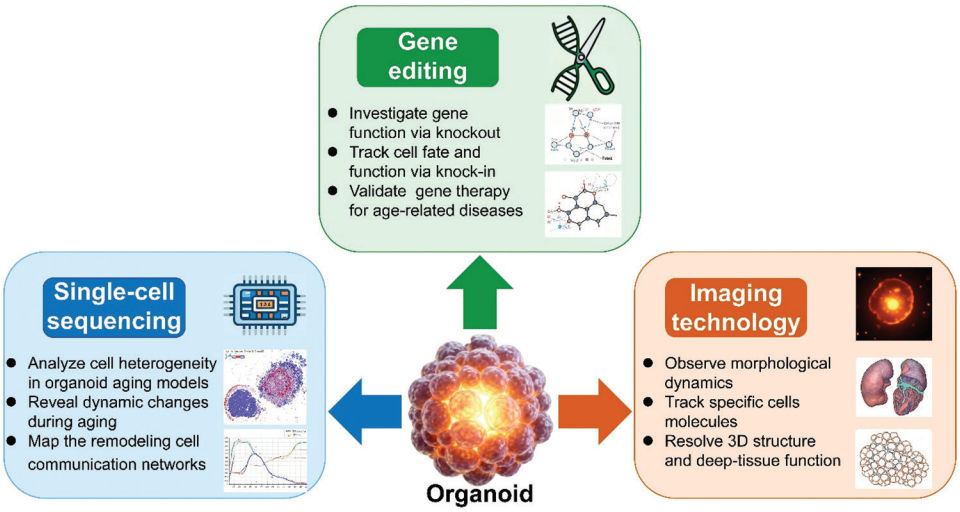

Figure 6. The combination of organoids and emerging technologies. The graphical elements were produced with the assistance of the AI tool Gemini, while the overall mechanistic diagram was constructed using Adobe Illustrator.

expression changes, and cell–cell interactions during aging. This combined approach not only advances understanding of the molecular mechanisms underlying aging but also provides a theoretical framework for the development of anti-aging interventions.

7.2. Organoids and gene editing technology

The advent of gene editing technologies, exemplified by the CRISPR–Cas9 system, has precipitated a renaissance in the utilization of organoids for aging research, thereby enabling more in-depth exploration of gene function and the mechanisms underlying aging. The CRISPR–Cas9 system comprises a Cas9 nuclease and a guide RNA. The guide RNA directs the Cas9 nuclease to recognize and cleave specific DNA sequences, thereby enabling gene knockout, knock-in, or site-directed mutagenesis.

The application of CRISPR–Cas9 technology to generate gene knockouts in organoids allows investigation of the effects of specific gene deletions on the aging process.[177] In intestinal organoids, knockout of the *Lgr5* gene, which is related to stem cell maintenance, using CRISPR–Cas9 technology has shown that the self-renewal capacity of intestinal stem cells is significantly reduced.[42,178] Consequently, the growth and differentiation of intestinal organoids are inhibited, and the expression of senescence-related markers is upregulated, indicating that the *Lgr5* gene plays a key role in maintaining the stemness of intestinal stem cells and delaying intestinal aging. Gene editing technology can also be used to perform gene knock-in in organoids, facilitating studies of gene function and aging mechanisms. For example, insertion of a fluorescent protein gene into a specific genomic locus enables real-time tracking of gene expression and cell fate changes within organoids.

In cardiac organoid studies, the green fluorescent protein gene has been knocked into the cardiac troponin T (*cTnT*) gene locus, enabling real-time monitoring of *cTnT* reporter expression. This approach enables intuitive observation of cardiomyocyte differentiation and maturation, as well as assessment of the effects of aging on myocardial function.[179] The application of gene editing technology in organoids also provides a novel platform for gene therapy research. The feasibility and efficacy of gene therapy for age-related diseases can be evaluated by repairing or regulating pathogenic genes in organoid models. In brain organoids carrying mutations associated with AD, CRISPR–Cas9 technology has been utilized to repair disease-associated mutations, resulting in observable changes in Aβ aggregation, tau phosphorylation, and neuronal survival. This work provides an important experimental foundation for the advancement of gene therapy strategies for AD.[130]

As shown in Figure 6, the integration of gene editing technology with organoid systems provides a precise and efficient approach for aging research. This strategy facilitates elucidation of the relationships between genes and aging and opens new avenues for the development of anti-aging therapies.

7.3. Organoids and imaging technology

Imaging technology plays a key role in the study of organoids. Imaging technologies enable real-time observation of organoid growth, development, and aging processes,[36,180] and allow visualization of cellular and molecular changes, thereby providing intuitive and dynamic information for aging research.[181]

Conventional light microscopy and specialized modalities (light-field microscopy) are commonly employed techniques in organoid imaging. The use of light field microscopy facilitates observation of overall morphological and structural changes in organoids. As the aging process progresses, light field microscopy has revealed a gradual increase in liver organoid volume. Concurrently, organoid morphology becomes irregular, and cellular arrangement tends to become disordered.[182] As shown in Figure 6, fluorescence microscopy uses fluorescent labeling techniques to visualize specific cell types, molecules, or signaling pathways within organoids. For example, green fluorescent protein-labeled genes can be introduced into intestinal organoids. By labeling stem cell-specific genes with fluorescent proteins, changes in stem cell fate during aging can be tracked, and the dynamic processes of proliferation, differentiation, and senescence can be observed.[179]

With its high resolution and optical sectioning capability, confocal microscopy enables 3D imaging of organoids, clearly showing their internal cellular structure and molecular distributions. In studies of brain organoids, confocal microscopy has been used to observe age-related changes in neuronal synaptic connections, such as reductions in synapse number and abnormal synaptic morphology, providing important insights into the pathogenesis of neurodegenerative diseases.[183]

With continued advances in imaging technology, newer techniques such as multiphoton microscopy and light-sheet microscopy have been increasingly applied to organoid research.[184] Multiphoton microscopy allows deep tissue imaging while reducing phototoxicity, making it suitable for long-term observation of dynamic changes in organoids.[185] This technique can be used to monitor cardiomyocyte contraction and relaxation in cardiac organoids and their age-related alterations in real time, thus enhancing understanding of the mechanisms underlying age-associated declines in cardiac function. Light-sheet microscopy is characterized by high imaging speed and low phototoxicity, enabling acquisition of high-resolution,

3D images of entire organoids. These advantages provide comprehensive data for studying organoid development and aging processes. In renal organoid studies, light-sheet microscopy has been demonstrated to clearly visualize age-related structural and functional changes in renal tubules, offering a valuable platform for investigating age-related renal diseases.[186]

The integration of imaging technologies with organoid systems provides abundant visual information for aging research, deepens understanding of biological changes during aging, and promotes advances in the field of aging biology.

8. Conclusion

8.1. Core advantages of organoid systems in aging research

Organoids, endowed with unique biological and technical merits, have emerged as irreplaceable *in vitro* models for deciphering the multifaceted mechanisms of aging. A paramount advantage lies in their superior physiological fidelity to native tissues, a feature unattainable in conventional experimental systems. Unlike 2D cell cultures—in which natural cellular architecture is disrupted and niche-dependent microenvironmental signals are attenuated—organoids fully recapitulate the 3D structural hierarchy, cellular heterogeneity, and tissue-specific functional phenotypes of endogenous organs.[13] For instance, intestinal organoids spontaneously self-organize into crypt–villus architectures, harboring specialized lineages such as absorptive enterocytes, goblet cells, Paneth cells, and enteroendocrine cells. This structural consistency facilitates the investigation of age-related intestinal pathologies, including disruption of epithelial tight junctions (a primary contributor to enhanced intestinal permeability in the elderly) and decline in Paneth cell antimicrobial activity. These phenomena cannot be replicated in 2D monolayer cultures due to the absence of niche cues.[16,42,44,99] This fidelity also extends to neural research. Cerebral organoids develop stratified cortical domains, hippocampal-like structures, and functional synaptic connections, enabling quantification of age-dependent alterations in neural progenitor migration, synaptic density, and electrophysiological activity. These features are critical for elucidating neurodegenerative aging mechanisms in AD and PD. Importantly, the high physiological relevance of organoid-derived findings enhances translational relevance for human aging compared with 2D cultures or animal models, which often exhibit species-specific differences.[122,187,188]

A second core advantage of organoid systems is their capacity to elucidate complex cell–cell and cell–ECM interactions that underpin tissue aging. Aging is not driven by isolated cellular dysfunction but instead arises from dysregulated signaling networks among heterogeneous cell populations and their microenvironment. Organoid models preserve these interactions in an intact and physiologically relevant manner.[189,190] In hepatic organoids, for example, hepatocytes, cholangiocytes, and HSCs engage in bidirectional paracrine communication. HSCs secrete ECM components that modulate hepatocyte metabolic functions, while hepatocytes release cytokines that regulate HSC activation.[84,131] During aging, organoids accurately recapitulate pathological rewiring of these interactions, wherein excessive HSC activation drives aberrant ECM deposition and fibrosis, ultimately impairing hepatocyte viability and function. This process closely mirrors age-related hepatic fibrosis observed in humans.[191] Such models not only capture physiological signaling balance but also reveal how age-related signaling imbalances accumulate to drive tissue dysfunction, a dimension that remains elusive in simplified 2D systems.

Furthermore, organoids have proven highly effective in personalized precision aging research by addressing the inherent heterogeneity of human aging. Patient-derived organoids (PDOs) and iPSC-derived organoids are particularly valuable because they retain the genetic background, epigenetic signatures, and disease-specific traits of the donor. This property enables tailored investigations and offers unique opportunities to gain deeper insights into complex biological processes and diseases.[192-196] For example, iPSC-derived cerebral organoids from patients with Hutchinson–Gilford progeria recapitulate hallmarks of accelerated aging, including premature telomere attrition, nuclear lamina abnormalities, and hyperactivation of the SASP.[197] Clinically, PDOs derived from elderly cancer patients support *in vitro* drug sensitivity testing. High positive predictive values for chemotherapeutic responses, such as to the folinic acid–fluorouracil–oxaliplatin regimen in colorectal cancer, help avoid ineffective regimens and minimize adverse reactions, thereby advancing precision oncology in geriatric populations.[198]

8.2. Inherent challenges and limitations constraining organoid utility

Despite their transformative potential, organoid technology faces interconnected challenges that limit its application in aging research. Standardization, stability, and reproducibility are the most pressing obstacles.[13] Inter-laboratory variability in protocols—including donor-dependent epigenetic heterogeneity of iPSCs, region-specific differences in primary tissue isolates, batch-to-batch inconsistencies in medium, and compositional ambiguity of ECM scaffolds—causes substantial heterogeneity in organoid quality and function. For example, studies of intestinal organoid stem cell proliferation reported

a 2–3-fold inter-laboratory variation in 5-ethynyl-2′-deoxyuridine incorporation rates, attributed to fluctuations in R-spondin 1.[199] It is evident that even within a single laboratory, discrepancies in reagent batches (e.g., ECM protein composition) or culture conditions (e.g., oxygen tension modulating hypoxia-inducible factor signaling) have the capacity to influence cell growth kinetics and the initiation of senescence. This variability has the potential to compromise the validity of long-term aging studies. The tracking of telomere attrition across multiple passages, or the evaluation of anti-aging interventions, frequently yields irreproducible results, thereby delaying consensus on the mechanisms of aging.

Lack of vascularization represents a pivotal technical bottleneck. Native organs rely on vascular networks for oxygen/nutrient delivery and waste removal—a feature absent in current organoids.[173] This imposes two critical limits: organoids reach only 500–1,000 μm in diameter before central necrosis due to inadequate diffusion, precluding studies of age-related phenotypes requiring mature, large-scale tissues (e.g., age-related hepatic steatosis with intralobular fat accumulation). Furthermore, it has been demonstrated that this limitation disrupts endothelial–matrix signaling. Indeed, endothelial cells secrete vascular endothelial growth factor and angiopoietins to regulate stem cell activity, and their absence has been shown to perturb tissue homeostasis. Despite the exploration of angiogenesis strategies (e.g., HUVEC co-culture, microfluidic scaffolds, *in vivo* transplantation), these approaches remain experimental. Co-cultures achieve ≤30% vascular integration, and transplanted organoids often lose tissue-specific traits due to immune rejection or niche interference.[200] For instance, in the context of investigating age-related cardiovascular decline, contemporary organoids are inadequate for simulating myocardial cell senescence, a phenomenon accelerated by hypoxia and constituting a pivotal clinical manifestation.[201]

A third major challenge is incomplete immune reconstitution.[94] Conventional organoids lack functional immune compartments, including immune cells (e.g., T cells, macrophages, microglia) and soluble mediators (e.g., cytokines, chemokines). This precludes the simulation of immune aging processes—immunosenescence (age-related immune cell dysfunction) and inflammaging (chronic low-grade inflammation)—which drive tissue aging and age-related diseases.[202] In studies of elderly influenza susceptibility, for instance, lung organoids lacking alveolar macrophages cannot replicate the age-related decline in pathogen clearance.[203] In tumor immunology, elderly patient-derived tumor organoids fail to recapitulate immune–tumor crosstalk (e.g., programmed cell death protein 1/programmed death-ligand 1 activation), hindering the development of geriatric immunotherapies. While recent advances (e.g., peripheral blood mononuclear cell implantation in brain organoids, iPSC-derived microglia co-culture) show promise, they cannot replicate tissue-specific immune niches (e.g., gut-associated lymphoid tissue) or age-related immune functional decline.[204]

Despite the rapid expansion of organoid applications in drug screening, gene editing, and advanced imaging, significant limitations continue to hinder their translational readiness. Incomplete maturation remains a primary barrier, as most organoids retain fetal-like molecular signatures and lack adult-stage metabolic and electrophysiological complexity.[205] The absence of vascular and immune components restricts physiologically relevant nutrient delivery, intercellular communication, and inflammatory dynamics, all of which are essential for modeling disease trajectories. Scalability represents another obstacle; producing large, standardized batches with consistent quality is challenged by donor-specific variability, iPSC epigenetic memory, and lot-to-lot differences in matrices such as Matrigel. Long-term culture introduces additional biosafety and ethical considerations, including the accumulation of somatic mutations, chromosomal instability, and epigenetic drift, which complicate data interpretation. Future progress will depend on integrating vascularized organoid-on-chip systems, immune co-cultures, chemically defined matrices, good manufacturing practice-compliant manufacturing workflows, and rigorous genomic monitoring.[206] These advances are crucial for transitioning organoids from powerful exploratory models to reliable platforms capable of supporting clinical translation.

8.3. Innovative future directions to advance organoid technology

To surmount these challenges, two interdisciplinary strategies have been developed, leveraging breakthroughs in bioengineering and data science. The initial focus is on multi-organoid systems, otherwise referred to as "organ-on-a-chip" platforms, which integrate two or more organoid types. The purpose of this integration is to facilitate the study of systemic aging interactions.[207,208] Aging is a systemic process in which organ crosstalk via paracrine/endocrine/metabolic signals drives decline; however, single-organoid models are not capable of replicating this phenomenon. Multi-organoid systems incorporating biomimetic microfluidic channels have been shown to replicate physiological flow, nutrient gradients, and paracrine signaling. For instance, a liver–kidney–heart platform delineates how age-related fatty liver disrupts renal waste clearance and cardiac energy metabolism through altered fatty acid oxidation, mimicking comorbidities associated with age-related metabolic syndrome. Previous studies have explored the complex relationship between

the gut and the brain in the context of AD, revealing how age-related dysfunction of the gut barrier promotes the translocation of microbial metabolites, which in turn leads to neuroinflammation in brain organoids. Integrating PDOs into these systems will enable personalized whole-body aging trajectory studies, explaining why some individuals develop comorbidities (e.g., AD and type 2 diabetes mellitus) while others exhibit healthy longevity.[209]

The second strategy involves integrating deep artificial intelligence and machine learning (AI/ML) in a manner that is revolutionary for the analysis and optimization of aging research data. The substantial multidimensional datasets generated by organoids (e.g., single-cell transcriptomes, SA-β-gal time-lapse imaging, metabolomic profiles, and electrophysiological data) exceed the analytical capacity of conventional methods. AI/ML has been demonstrated to add value in three key ways:

(i) Mechanism discovery: ML models integrate multi-omics data to identify novel aging pathways. For example, convolutional neural networks quantify age-related changes in neural progenitor migration and synaptic density in brain organoids,[210] while transformer models map genome-wide DNA methylation to senescence onset. In AD research, an ML model trained on brain organoid electrophysiological data identified reduced gamma synchrony as an early warning signal for tau hyperphosphorylation.[211]
(ii) Culture optimization: Reinforcement learning can iteratively adjust culture parameters (e.g., growth factor ratios, ECM stiffness, oxygen tension) to enhance maturity and reduce variability.[212]
(iii) High-throughput drug screening: AI correlates compound structure with phenotypic readouts (e.g., SA-β-gal activity and telomere length).[213] In one study, AI analysis of more than 1,000 compounds identified novel anti-aging drugs, thereby accelerating preclinical development.[214]

8.4. Translational impact on aging research and clinical geriatrics

Organoid technology drives progress in anti-aging science and clinical care across three domains. In basic aging biology, organoids enable the dissection of tissue-specific mechanisms and the distinction between conserved and tissue-specific drivers. Comparative analyses of skin, liver, and brain organoids demonstrate that universal hallmarks (e.g., telomere attrition and p16INK4a upregulation) vary in their rate of progression: Telomere shortening is two- to three-fold faster in skin keratinocytes than in HSCs, explaining the earlier onset of skin thinning relative to liver fibrosis.[25,174]

In anti-aging drug development, organoids serve as valuable preclinical models. Unlike 2D/animal models, which are poor predictors of human efficacy and toxicity, organoids more faithfully replicate human tissue physiology. For example, a retinal organoid study identified quercetin 3-O-glucoside as an inhibitor of retinal pigment epithelial senescence through nuclear factor erythroid 2-related factor 2–antioxidant response element activation, a finding subsequently validated in mouse models of age-related macular degeneration.[165] Furthermore, organoids have been demonstrated to enable the assessment of age-specific toxicity. Hepatic organoids derived from elderly donors, for instance, revealed that mTOR inhibitors increase hepatocyte apoptosis, thus guiding dose adjustments in geriatric patients. In a preliminary clinical study, the implementation of organoid-based screening resulted in a 40% reduction in the number of candidate compounds requiring further investigation, accompanied by significant time and resource savings.[215]

In the clinical management of age-related diseases, organoids represent a significant advancement in personalized medicine and regenerative therapy. Patient pathology is recapitulated by PDOs of AD, type 2 diabetes mellitus, and cardiovascular disease. One study revealed that the capacity of AD brain organoids to exhibit patient-specific Aβ clearance efficiency is associated with the presence of anti-Aβ antibodies, a finding with important clinical implications, as it enables clinicians to identify subpopulations likely to respond to treatment.[21] In oncology, PDO-based drug sensitivity testing increased chemotherapy efficacy in elderly colorectal cancer patients while reducing severe adverse reactions. Beyond drug testing, regenerative medicine applications are particularly promising: iPSC-derived corneal organoids from patients with keratoconus differentiated into functional epithelial cells that restored vision in preclinical animal models, paving the way for autologous therapy for age-related tissue damage.[216]

In conclusion, organoids—with physiological fidelity, capacity to resolve intercellular interactions, and potential for personalization—represent a cornerstone of modern aging research. While challenges related to standardization, vascularization, and immune reconstitution persist, advances in multi-organoid systems and AI integration are expected to drive progress. Their translational impact—from advancing basic biology to accelerating drug development and enabling personalized clinical care—has the potential to transform our understanding of aging and our ability to extend healthspan.

Acknowledgments

None.

Funding

This work was supported by the National Natural Science Foundation of China (Grant Nos. 82125023 to Hui Xie;

82272562 and 82472523 to Zhen-Xing Wang), the Science and Technology Innovation Program of Hunan Province (Grant No. 2023RC3075 to Zhen-Xing Wang), and the Hunan Provincial Innovation Foundation for Postgraduate (Grant No. CX20250357 to Yu Yang).

Conflict of interest

Hui Xie is an Associate Editor of this journal and Guest Editor of this special issue but was not involved, directly or indirectly, in the editorial or peer-review process for this manuscript. Separately, other authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

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