

Catilage organoid model of age-related ostoarthritis to study intervention strategies

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Abstract

Aging is an inevitable biological process in nature. As aging progresses, physical functions continue to decline, eventually leading to aging-related diseases. It is urgent to find effective ways to prevent and treat aging-related diseases. The use of organoids to study the development of aging-related diseases is based on the fact that they retain the physiological structure and functional characteristics of their origin, compensating for the fact that the complexity of human aging-related diseases cannot be reproduced in animals, cells, yeast, and *Caenorhabditis elegans*. Osteoarthritis (OA) is a common aging-related musculoskeletal disease, and chondrocyte senescence is one of the major risk factors for OA. Therefore, it is necessary to construct cartilage organoids to model OA. This brief review describes the cell source, culture environment, and intervention methods of cartilage organoids, providing insights for future drug screening and treatment of OA.

Keywords: Aging, osteoarthritis, cartilage organoid

It is widely accepted that aging is an inevitable and normal physiological phenomenon [1]. Aging generally begins after sexual maturity, and there is a steady decline in bodily functions as we age, eventually leading to the onset of a variety of diseases [2]. It is now generally accepted that aging is one of the major risk factors for the development of aging-related diseases [3]. Nowadays, the global

economic burden of aging-related diseases is increasing due to increasing longevity and aging population, and it is urgent to develop effective prevention and treatment strategies [1]. Researchers have mainly established models of aging-related diseases in animals, cells, yeast, and *Caenorhabditis elegans* for their studies. However, it is unclear how well these models reflect the complexity of human aging [4].

Organoids are multicellular clusters formed by *in vitro* 3D culture of stem cells that mimic the physiology and cellular composition of real tissues or organs [4, 5]. Organoids retain the structural and functional properties of their origin and are capable of self-renewal and self-organization [5]. Genetic and pharmacological manipulations in organoids, which reflect the complex cellular environment of human biology, provide the opportunity to study organ development and the early stages of disease pathogenesis. In many aspects of preclinical drug development, animal and *in vitro* models are complemented by organoids (Table 1) [4]. For example, patient-derived tumor organoids retain the genetic and phenotypic heterogeneity in the original tumor, which predicts patient response to different drugs and provides a basis for personalized treatment [6]. Based on the differences between mouse and human brains,

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Table 1. Advantages of organoids.

Organoids	Advantages	References
Intestinal organoid	To assess drug absorption	[46]
Brain organoids	To address the differences between human and mouse brains	[47]
Non-small cell lung cancer organoids	For drug screening biomarker identification	[48]
Heart organoids	To assess the toxic effects of drugs on the heart	[49]
Liver organoids	To model liver regeneration, to study the toxic effects of drugs on the liver, and to address the shortage of liver donor transplants	[50, 51]
Skin organoids	To study the mechanism of human skin regeneration.	[52]

brain organoids were used to mimic brain diseases such as Alzheimer's disease, glioblastoma, Parkinson's disease, primary microcephaly [7]. Therefore, organoids may be a new promising tool to model changes in the aging process and to study the onset of aging-related diseases.

The Global Burden of Disease in 2017 (GBD 2017) study found that aging-related diseases accounted for 92 out of 293 (31.4%), including neurodegenerative diseases, cancer, cardiovascular diseases, immune system diseases, metabolic diseases, musculoskeletal disorders, *etc* [8, 9]. The elderly are more susceptible to injuries and degenerative musculoskeletal disorders than the young [9]. Osteoarthritis (OA), which affects more than 80% of people over the age of 65, causes disability in the elderly and is costly to patients and society [10, 11]. Chondrocyte loss and aging contribute to the development of OA [11]. Therefore, it is necessary to generate cartilage organoids to establish OA disease models [12]. This paper reviews the cell sources, culture environments, and management of disease-mimicking cartilage organoids to provide insights for future drug screening and treatment of OA.

Construction of OA

Table 2. Cell source of cartilage organoids.

Cell resources	methods	Reference
MSCs	0.1 μ M dexamethasone, 40 μ g/mL L-proline, ITS, 50 μ g/mL ascorbic acid 2-phosphate and 10 ng/mL TGF- β 3	[18]
iPSCs	1% L-glutamine, 1% non-essential amino acids, 1% sodium pyruvate, 1% ITS-X, 50 μ g/mL ascorbic acid, 0.1 mM 2-mercaptoethanol, 10 ng/mL human basic fibroblast growth factor, 10 ng/mL TGF- β 1, 10 ng/mL bone morphogenetic protein-2 (BMP-2), 10 ng/mL growth differentiation factor 5 (GDF5)	[53]
ESCs	0.1 μ M LDN193189, 10 μ M SB431542, 3 μ M CHIR99021, 10 μ M ROCK inhibitor Y-27632, 20 ng/mL brain-derived neurotrophic factor, 100 ng/mL fibroblast growth factor 8 (FGF8), 20 ng/mL Shh, 20 ng/mL epidermal growth factor (EGF)	[54]
hPDCs	0.1 μ M ascorbate-2 phosphate, 0.1 μ M dexamethasone, 40 μ g/mL proline, 20 μ M ROCK inhibitor Y-27632, ITS+, 100 ng/mL BMP-2, 100 ng/mL GDF5, 10 ng/mL TGF- β 1, 1 ng/mL BMP-6, and 0.2 ng/mL basic FGF2	[55]
MPCs	0.1 μ M dexamethasone, 40 μ g/mL L-proline, 10 μ g/mL ITS, 50 μ g/mL ascorbic acid and 10 ng/mL TGF- β 1/	[17]
iMPCs	TGF- β 3	[19]

The cell sources, culture environments, and intervention approaches used to construct cartilage organoids are important factors in simulating the disease state of OA.

Cell sources

Organoids are usually established from stem cells or patient-derived induced pluripotent stem cells (iPSCs) [13]. Healthy human chondrocytes can only be obtained under special conditions according to the principle of no harm. For example, cartilage debris from patients can be used as a cellular source for cartilage organoids only after obtaining informed consent from the amputee patient and official ethical approval [14]. Since it is difficult to obtain healthy chondrocytes from human samples, stem cell induction is commonly used to construct cartilage organoids, most commonly using mesenchymal stem cells (MSCs) and iPSCs [14]. Various techniques and methods are available to induce differentiation of MSCs into chondrocytes, adipocytes, and osteoblasts [15, 16], but only iPSCs can differentiate into endothelial cells, osteoclasts, and other immune components. In addition to conventional stem cells, embryonic stem cells (ESCs), pluripotent cell lines, human periosteum-derived cells (hPDCs), and autologous digestive chondrocytes can also be used to construct cartilage organoids (Table 2) [12].

Additionally, progenitor cells were also used to construct cartilage organoids. For example, mesenchymal progenitor cells (MPCs) were cultured to form cartilage organoids by 10 ng/mL transforming growth factor β 1 (TGF- β 1)/TGF- β 3 promoted differentiation in a special serum-free medium containing 1% penicillin-streptomycin, 0.1 μ M dexamethasone, 40 μ g/mL L-proline, 10 μ g/mL ITS premix (insulin, transferrin, selenium, bovine serum albumin and linoleic acid), 50 μ g/mL ascorbic acid [17, 18]. MSCs are well-established chondrogenic progenitor cells [14], and iPSC-derived mesenchymal progenitor cells (iMPCs), MSC-like progenitor cells induced by iPSCs [19], can also be used as cells for constructing cartilage organoids.

The culture environment

Stem cells are induced to proliferate, differentiate, and form organoids in specialized culture environments as required for the growth and development of tissues and organs. The complex network structure of the extracellu-

lar matrix (ECM), synthesized inside the cell and secreted outside, could not be formed without its polysaccharide and protein components, including collagen, elastin, laminin, fibronectin, glycosaminoglycans, and other macromolecules [20]. In addition, cell adhesion, proliferation, spreading, differentiation, binding, tissue structure stability, and physiological activities of cells depend on growth factors, cytokines, and chemokines released from the ECM [21]. Therefore, stimulating the properties of ECM in biological tissues is an essential strategy to achieve a better culture environment for organoids. Several ECM-derived materials, such as matrigel and hydrogel, have been used for organoid culture. For example, silk fibroin-based hydrogel was used to construct cartilage organoids to detect biological and physical signals [22]. Type I collagen hydrogel was used to construct cartilage organoids without growth factors [23]. The porcine and human kidney dECM-derived hydrogels promote the formation of an endogenous vascular within the time course of kidney organoid differentiation [24]. Growth factors also play an important role in promoting the proliferation and differentiation of stem cells into organoids [12]. The common growth factors are EGF, FGF, and TGF- β . Liver organoids requires EGF, hepatocyte growth factor, and FGF receptors [25]. EGF and bFGF promote adipose-derived stem cells differentiated into mature neural cells rather than osteocyte lineage cells [26]. TGF- β is a potent inducer of stem cell differentiation to form cartilage organoids, smooth muscle cells, immature cardiomyocytes [27]. Thus, growth factors contribute to the differentiation of stem cells to form different organoids.

Currently, scaffold-based and scaffold-free are the two main methods for cartilage organoid culture. Scaffold-based is the self-assembly of biomaterials with multiple holes into multilayered organoid structures along specific spatiotemporal directions to support cell adhesion and proliferation [12]. Matrix gels and hydrogel materials are used not only as cell culture media to provide special conditions for organoids, but also as temporary scaffolds to maintain the stability of organoid structures [28]. The scaffold-based culture method can help cells proliferate and differentiate to form organoids more effectively. For

example, a 3D culture system by using collagen gel matrix system increased germ cell viability, meiosis, and post-meiotic differentiation into presumptively differentiated spermatocytes [29]; whereas a culture system by single-cell suspensions blocked the meiosis in spermatogenesis and inhibited spermatogenesis [30]. Scaffold-based pancreatic cancer models reflect drug efficacy better than scaffold-free pancreatic cancer models [31]. In scaffold-free culture, organoids are grown by placing cells in suspension culture or by growing spherical scaffolds [32]. The advantages of scaffold-free culture include simplicity, reproducibility, massive cell proliferation, and rapid organoid formation [12]. A study showed that the scaffold-free pancreatic cancer organoid model formed a mature circular structure after culture for 24 h, while the scaffold-based model showed stable formation and high viability after culture for 7 days [31]. A comparison of scaffold-free and scaffold-based reconstructed human skin models showed that the scaffold-free skin model has a higher self-renewal capacity than the scaffold-based skin model cells [33]. Figure 1 shows the establishment of cartilage organoids.

Simulation of OA

The organoids of full-thickness cartilage tissue removed from smooth-appearing portions of the tibial plateau and femoral condyles of OA patients were smaller in diameter than the ND (non-degenerate) group, but both groups were abundant in proteoglycans and collagen and did not differ in macroscopic appearance in alginate gels [34]. This suggests that OA chondrocytes may have similar characteristics to healthy chondrocytes under the same culture conditions. Therefore, it is necessary to establish additional conditions for the intervention of organoids to better mimic OA. Currently, there are four methods to simulate OA in organoids: cytokines, mechanical stress, microenvironment and genetic modeling.

Mechanical loading

Hyperphysiologic mechanical loading is one of the important factors in the development and progression of OA [13, 35]. Niek G. C. Bloks *et al.* mechanically loaded spheri-

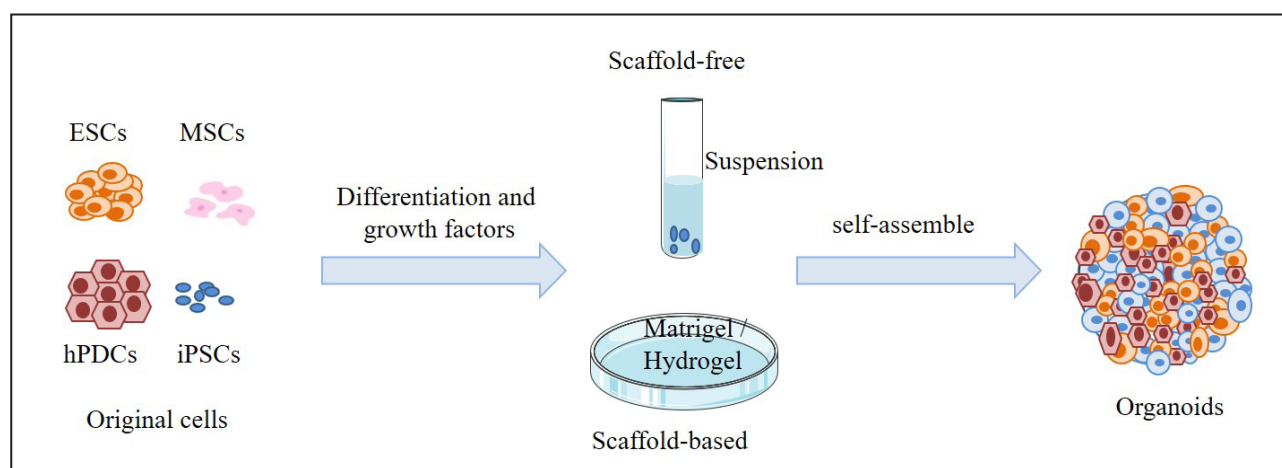


Figure 1. Construction of cartilage organoids.

cal neocartilage constructs using a MACH-1 mechanical testing device (Biomomentum, Laval, Canada) with parameters set to a loading rate of 5 Hz, a sinusoidal peak strain of 20%, and a duration of 10 min (Figure 2). For the cylindrical constructs, a customized loading device was used with the same loading parameters. The mechanically loaded cartilage organoids were placed in TGF- β -free CD medium to prevent their anabolic responses from being perturbed by mechanical loading [35]. The results showed changes in the expression of genes such as CD44, ITGA5, and CAV1, which are associated with anatomical morphogenesis and wound healing response. This confirms that supra-physiological mechanical loading leads to detrimental changes in the phenotypic state of chondrocytes, resulting in OA disease. Therefore, mechanical loading may trigger the onset of OA.

Cytokines

Cytokines are the most commonly used induction modality because they are inexpensive and easy to customize and manipulate. Cytokines play a critical role in the pathogenesis of OA by mediating joint interface remodeling and altering joint hemostasis through chronic inflammation [35]. Diana M. Abraham *et al.* [36] treated organoids with recombinant IL-1 β (5 ng/mL) for 24 h to establish a skeletal inflammation model. It was found that only IL-1 β reduced the size of arthrocyte spheroids in a dose-dependent manner [37]. Laura Donges *et al.* [38] constructed OA cartilage organoids to which low concentrations of pro-inflammatory cytokine mixtures (50 pg/mL TNF- α , 50 pg/mL IL-1 β , and 100 pg/mL IL-6, INFL) were added during

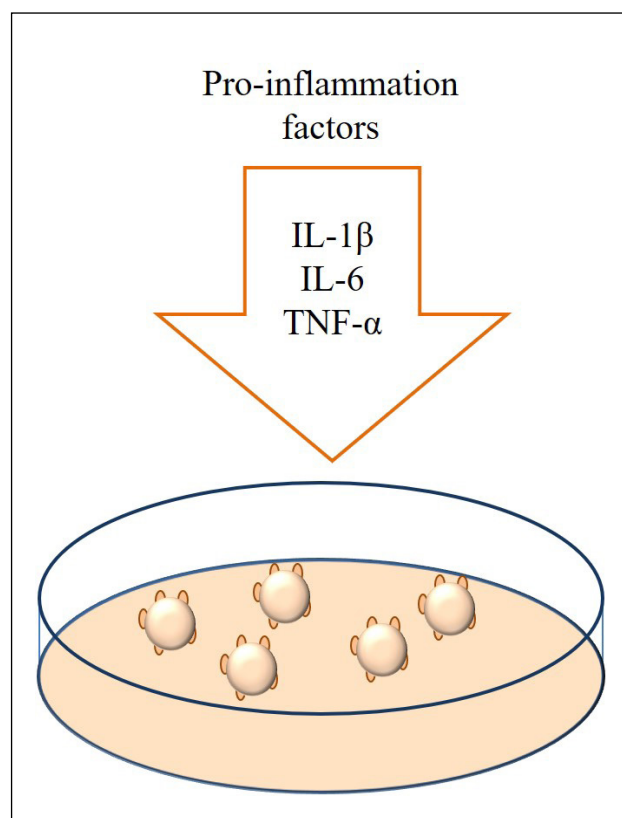


Figure 3. The production of OA by pro-inflammatory cytokines.

the hypertrophic culture phase. Figure 3 shows the induction of a cartilage organoid OA disease model with pro-inflammatory cytokines.

Microenvironment

The disadvantage of cartilage monotissue is the inability to reproduce native multi-tissue interactions. However, the reproduction of essential features of OA can be created in bioreactors and microfluidic devices for long-term culture [13]. Researchers have attempted to create a miniature joint system (miniJoint) with osteochondral, adipose, and fibrous analogues for the study of OA [39]. They first created the miniJoint. Adipose tissue (AT), synovial-like fibrous tissue (SFT), and osteochondral units (OC) were added to the miniJoint chamber, and adipogenic medium, fibrogenic medium, and osteogenic medium were used to maintain different tissue phenotypes. In particular, a universal medium (UM) simulated synovial fluid, which flowed to the bottoms of the different tissues and allowed tissue interactions. After 28 days of tissue co-culture, synovial-like fibrous tissues were treated with IL-1 β (10 ng/mL) to induce synovial inflammation, and ascorbic acid-2-phosphate (pVC), L-proline (Pro), and TGF- β 3 were excluded from the UM. After 3 days, a combined treatment of oligodeoxynucleotides and bone morphogenic protein-7 was added to all media to simulate “systemic” and “local” administration. Finally, after 4 days of therapeutic intervention, various methods were used to evaluate the therapeutic effect (Figure 4). The study demonstrated the ability of miniJoint for the development of disease-modifying drugs for OA [49].

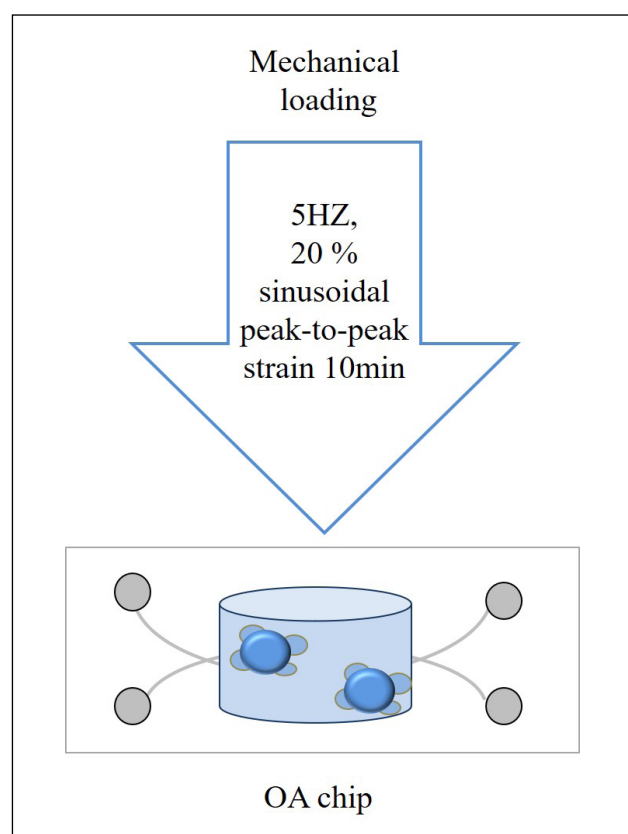


Figure 2. The generation of OA by mechanical loading.

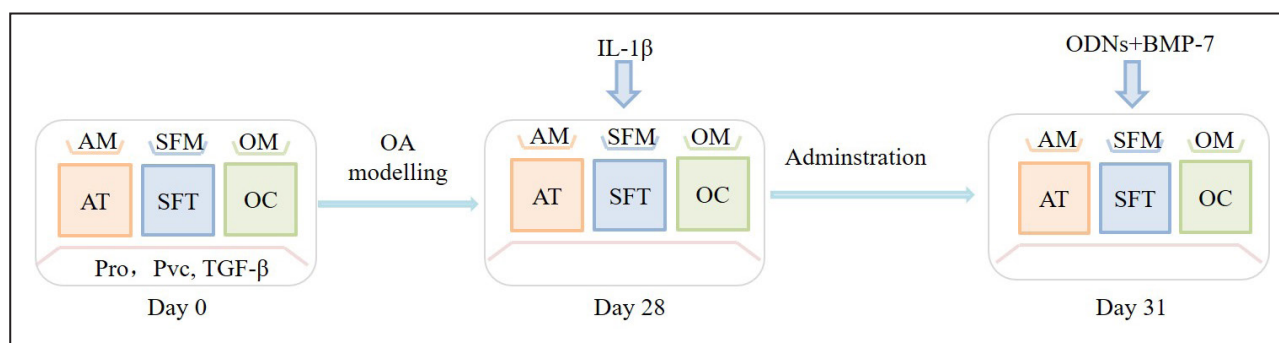


Figure 4. The experimental procedure of creating OA model in the miniJoint.

Genetic modeling

In addition, gene editing techniques such as CRISPR-Cas9 can be used to introduce gene mutations associated with OA into cartilage organoids to mimic OA [40]. For example, Niek GC Bloks *et al.* used CRISPR-Cas9 establish collagen type VI alpha 3 chain (COL6A3) mutant hiPSCs cells and then COL6A3 mutant hiPSCs cells were differentiated to form cartilage organoids to model OA [41].

Furthermore, growth factors (*e.g.*, hypoxia-inducible factor 2 α (HIF-2 α)) and chemically induced enzymes (*e.g.*, ECM catabolic enzymes) can also induce OA. Significantly elevated of HIF-2 α in human and mouse OA chondrocytes enhanced Fas expression and caspase activity, which promotes chondrocyte apoptosis and OA [42]. Monosodium iodoacetate induces chondrocyte death resembling the pathological changes of human OA [43]. But they have only been applied in 2D models and therefore require further development for application.

The applications of cartilage organoids in OA

There are many OA models available for drug screening and OA related studies. Vincent P Willard *et al.* [44] treated iPSCs-derived cartilage organoids with IL-1 α to mimic OA for drug screening, and found that the nuclear factor kappa-B inhibitor SC-514 was the most effective candidate to protect cartilage organoids, which effectively reduced cartilage loss, matrix metalloproteinases production, nitric oxide production, and prostaglandin E2 production. The cartilage organoids treated with IL-1 β were used to test the protective effect of the adenosine 2a receptor agonist against OA [36]. Implantation of cartilage organoids in the body contributes to cartilage defect repair and treat OA [45].

Since animal and cellular models cannot reflect the complex mechanisms of human aging, organoids are used to study aging-related diseases. For OA, one of the most common diseases of aging, the construction of cartilage organoid OA models is essential. In this paper, we summarized the cell sources, culture environments, and intervention methods of cartilage organoids, which facilitates the development of cartilage organoids for modeling OA and the development of new methods for treating OA.

Declarations

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