SOMATO PUBLICATIONS

ISSN: 2689-8659

Annals of Stem Cell Research

Review Article

Chondrogenic Potential of Synovium-Derived Progenitor Cells in Three-Dimensional Culture: A Review

Toth E[1*], Hofer S[2] and Teixeira T[3]

[1]Department of Orthopaedic Research, Semmelweis University, Budapest, Hungary

[2]Department of Biomedical Engineering, University of Innsbruck, Innsbruck, Austria

[3]Department of Regenerative Medicine, University of Lisbon, Lisbon, Portugal

*Address for Correspondence: Eszter Toth, Department of Orthopaedic Research, Semmelweis University, Budapest, Hungary; E-mail: eszter.toth@semmelweisuniversity.edu

Received: 20 April 2022; Accepted: 29 July 2022; Published: 11 November 2022; DOI: 10.5281/zenodo.22237773

Citation of this article: Toth E, Hofer S, Teixeira T (2022) Chondrogenic Potential of Synovium-Derived Progenitor Cells in Three-Dimensional Culture: A Review. Ann Stem Cell Res, 5(1): 01-06.

Abstract

Background: Synovium-derived mesenchymal stromal cells outperform other adult sources in cartilage-forming assays, and three-dimensional culture is required for a chondrocytic phenotype at all.

Objective: To review the evidence for synovial superiority, the three-dimensional systems used, and the hypertrophy that limits it.

Methods: Narrative review of studies comparing mesenchymal sources for chondrogenesis and of three-dimensional culture of synovial cells.

Findings: Synovium yields roughly a hundredfold more colonies per nucleated cell than bone marrow, and retains chondrogenic capacity where other sources lose it. Hypoxia at 5% oxygen raises SOX9, COL2A1 and ACAN 1.4- to 2.3-fold while suppressing COL10A1, though one three-way comparison found bone marrow cells deposited the most glycosaminoglycan.

Conclusions: The case for synovium rests on yield and retained potency rather than a ceiling advantage in matrix quality. Suppressing hypertrophy, not selecting a source, is the limiting step.

Keywords: synovium; mesenchymal stromal cells; chondrogenesis; three-dimensional culture; hypertrophy

Introduction

Articular cartilage does not repair itself. It is avascular, aneural and sparsely populated by slowly turning-over cells, so a full-thickness defect fills with fibrocartilage rather than hyaline cartilage. Cell therapy has been pursued for four decades, and the choice of cell is still open.

Multipotent mesenchymal cells meeting the standard identity criteria of plastic adherence, surface phenotype and trilineage differentiation [1] were isolated from adult human synovial membrane [2], and a matched comparison across five human tissues then found synovium the superior source for chondrogenesis [3]. That finding has largely held, though synovium is no more accessible than bone marrow or fat and is harvested arthroscopically rather than as surgical waste.

Cells expanded in monolayer do not make cartilage. Chondrogenesis requires a three-dimensional configuration — classically a centrifuged pellet [4,5] — in which cells round up and deposit a matrix.

Materials and Methods

Studies were retrieved from PubMed, Europe PMC and Crossref for the terms *synovium-derived*, *synovial mesenchymal stem cell*, *chondrogenesis*, *pellet culture*, *hypoxia* and *hypertrophy*, without date restriction. Priority went to comparisons of synovium against other mesenchymal sources under matched conditions and to three-dimensional studies reporting quantified matrix outcomes. Records were confirmed against Crossref or the publisher.

Why synovium

The comparative case rests on three distinct properties.

The first is yield. In a matched rat comparison across bone marrow, synovium, periosteum, adipose tissue and muscle, synovium gave approximately a hundredfold higher colony number per nucleated cell than bone marrow [6].

The second is retained potency after expansion. In the eight-donor human comparison, marrow, synovium and periosteum all proliferated to passage 10, but synovium retained chondrogenic capacity most consistently [3]. Within synovium the subregion matters — fibrous and adipose synovium both outperform subcutaneous fat [7], and fibrous synovium releases more cells in a suspended culture model [8].

The third is lineage proximity. Cells from synovium, meniscus, anterior cruciate ligament and articular chondrocytes share broadly similar gene expression profiles [9]. In vivo rabbit comparison supported the same ranking [10], and the tissue has been reviewed as a cartilage-specific stem cell source [11].

The case is not unanimous. A three-way comparison of bone marrow, synovial membrane and synovial fluid found glycosaminoglycan deposition at day 28 highest in bone marrow cells at 190 µg per sponge, against 160 for synovial membrane and 118 for synovial fluid, with chondrogenesis and hypertrophy both more pronounced in the marrow cells [12]. With the yield data, the honest summary is that synovium wins on cells available and on consistency, not necessarily on peak matrix output per cell.

Three-dimensional systems

The pellet remains the reference configuration [4,5], and conditions for synovium-derived cells have been optimised against bone marrow-derived controls [13]. Growth factor requirements follow the general mesenchymal pattern: TGF-β family members drive the process, with BMP-2, -4 and -6 differing in their effect on cartilage formation [14], and TGF-β1 enhancing BMP-2-induced chondrogenesis in synovial explants

while arresting downstream differentiation at an early hypertrophic stage [15].

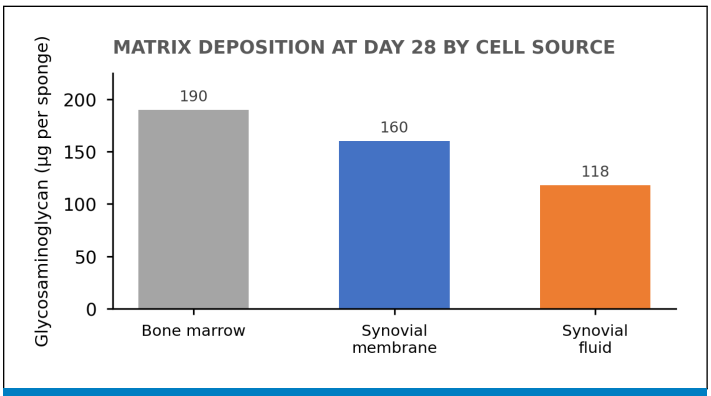

Figure 1: Glycosaminoglycan deposited per sponge at day 28 by cells from three sources under matched chondrogenic conditions. Bone marrow cells outperformed synovial ones on this endpoint. Data from Sekiya et al. [12].

Scaffold-free constructs from synovial cells have been used for cartilage repair [16] and developed into a next-generation repair system [17]; aggregates of synovial cells, roughly one millimetre in diameter after three days, are solid enough to handle and adhere to a defect, though high-density aggregates fail from nutrient limitation [18]. Decellularised stem cell matrix has also served as a substrate, where its antioxidant properties promote synovium-derived chondrogenesis [19]. In aged primates, autologous synovial aggregates in meniscal defects produced larger and histologically better menisci, and better femoral condyle cartilage, than the untreated contralateral knee at 16 weeks [20].

Oxygen and mechanical loading

Standard incubators run at atmospheric oxygen, far above the 1–7% articular cartilage experiences in vivo. At 5% oxygen against 21%, synovium-derived cells formed 2.5-fold more colonies at 18 days and upregulated SOX9 1.4-fold, COL2A1 1.6-fold and ACAN 2.3-fold, all significant, while strongly downregulating the hypertrophy marker COL10A1 [21]. That combination is unusual: most interventions that increase matrix genes also increase hypertrophy.

Table 1: Comparative studies of synovium against other mesenchymal sources for chondrogenesis.

Comparison	Species	Principal finding	Ref.
Five mesenchymal tissues	Human	Synovium superior for chondrogenesis; all reached passage 10	[3]
Five mesenchymal tissues	Rat	~100-fold higher colony yield per nucleated cell than marrow	[4]
Synovium subregions vs fat	Human	Fibrous and adipose synovium both exceed subcutaneous fat	[5]
Synovium, meniscus, ACL	Human	Similar expression profiles to articular chondrocytes	[6]
Four tissues, in vivo	Rabbit	Synovium among the better sources for defect repair	[8]
Marrow, membrane, fluid	Human	Marrow deposited most GAG (190 vs 160 vs 118 µg/sponge)	[27]

Mechanical loading is more equivocal and depends on timing. In agarose at 10 kPa and 0.25 Hz for one hour daily, compression from day 1 downregulated SOX9, COL2A1 and ACAN, whereas the same regimen delayed to days 21–28 increased matrix genes and suppressed hypertrophy [22].

Hypertrophy

The persistent problem is that mesenchymal chondrogenesis reproduces the growth plate rather than articular cartilage. Human mesenchymal cells undergoing chondrogenesis in vitro prematurely express hypertrophic markers, and constructs transplanted ectopically into immunodeficient mice calcify and are invaded by blood vessels [23].

Suppressing it is an active target, not a solved problem. Histone deacetylase 4 promotes TGF-β1-induced chondrogenesis of synovium-derived cells while inhibiting hypertrophy of the differentiated cells [24]. Articular chondrocytes achieve the same dissociation in coculture, secreting parathyroid hormone-related protein that lowers the COL10A1:COL2A1 ratio and alkaline phosphatase activity and abolishes calcification in vivo

[25]. Hypoxia acts in the same direction [21], as does delayed loading [22]. None has yet produced a stable articular phenotype that persists in vivo.

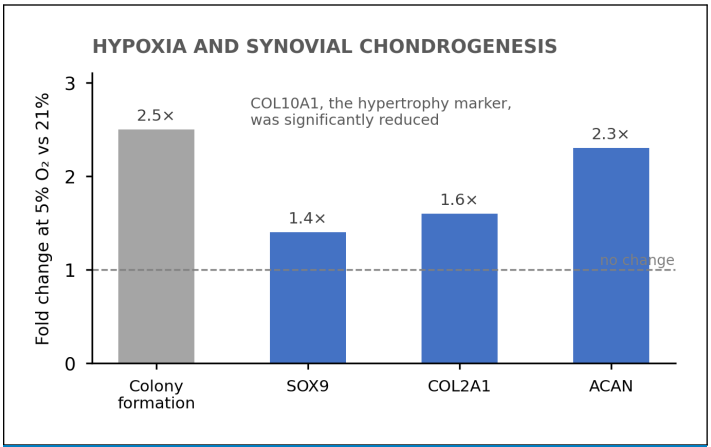

Figure 2: Effect of 5% oxygen against 21% on colony formation and chondrogenic gene expression in synovium-derived mesenchymal stromal cells. All changes significant at p < 0.05. Data from Bae et al. [21].

Donor status and clinical translation

A practical concern is whether cells from diseased joints are usable. Yields and chondrogenic potential of primary synovial cells are comparable between rheumatoid arthritis and osteoarthritis patients: 8.4 ± 3.9 against 8.0 ± 0.9 thousand nucleated cells per milligram of synovium, with no significant difference in pellet weight, sulfated glycosaminoglycan content or ACAN and COL2A1 expression [26].

Clinical experience is limited but encouraging. In ten patients with cartilage defects, a median 47 ± 21 million passage-0 synovial cells were held on the defect arthroscopically for ten minutes; at a median 48 months, MRI score improved from 1.0 ± 0.3 to 5.0 ± 0.7 and Lysholm score from 76 ± 7 to 95 ± 3, both significant, with hyaline cartilage in the deep zone in three of four patients who consented to second-look arthroscopy [27].

Discussion

First, the superiority of synovium is real but narrower than usually stated: it is superior in colony yield and in retention of potency through expansion, and at least one careful comparison found bone marrow cells depositing more matrix per construct.

Second, the three-dimensional environment is instructive rather than merely permissive, and its parameters have not been jointly optimised: oxygen tension, loading regimen and timing each change the outcome, and have mostly been studied one at a time.

Third, hypertrophy remains the limiting problem and is not source-specific. Any therapy built on mesenchymal chondrogenesis has to prevent the tissue from completing the endochondral programme, and no reported intervention yet does so reliably.

This is a narrative review without systematic search or risk-of-bias assessment. Endpoints differ widely — glycosaminoglycan is reported per pellet, per construct or normalised to DNA, preventing pooling — and several studies cited are rodent, bovine or porcine, so species confounds the comparative claims.

Conclusion

Synovium-derived progenitor cells are a well-supported choice for cartilage engineering, because they can be obtained in quantity and retain chondrogenic capacity through the expansion needed to reach a clinical dose. Three-dimensional culture is mandatory, and within it oxygen tension and the timing of mechanical loading are consequential and under-explored. The unresolved obstacle is hypertrophy: constructs generated this way express growth-plate markers and calcify in vivo, and until that programme can be arrested the tissue produced is not articular cartilage. Studies should report oxygen tension, loading history and hypertrophic markers alongside matrix outcomes, and normalise matrix content comparably between laboratories.

Acknowledgements

The authors thank the library staff who assisted with retrieval of the primary literature reviewed here.

Funding

This review received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Conflict of Interest

The authors declare that they have no competing interests relevant to the content of this review.

Ethics Statement

This article reviews previously published studies and contains no new studies with human participants or animals performed by any of the authors. Ethical approval was therefore not required.

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