

Praca poglądowa/Review paper

Cartilage Dynamics, Degeneration, and RepairMonika Rosochowicz^{1,2}, Katarzyna Kulcenty³, Wiktoria Suchorska^{2,3}¹Doctoral School, Poznan University of Medical Sciences Poznan, Poland²Department of Electroradiology, Poznan University of Medical Sciences, Poznan, Poland³Radiobiology Laboratory, Greater Poland Cancer Centre, Poznan, Poland

Abstract

Cartilage is a firm, avascular tissue that cushions joints and supports the skeleton, but because it has no blood supply or nerves, it has very limited ability to repair itself once damaged. Over time, ageing and mechanical stress disturb the balance between matrix formation and breakdown, pushing chondrocytes toward senescence, hypertrophy, and calcification – changes that underlie osteoarthritis, a joint disease driven by chronic inflammation and progressive cartilage loss. Current treatments range from pain relief and surgical procedures to chondrocyte-based implantation techniques, but none fully restores healthy cartilage function, and each has its own drawbacks. Stem cell therapies offer new possibilities but face obstacles such as tumour risk and ethical limitations, while conditioned medium, the secretome collected from cultured stem cells, has emerged as a cell-free alternative that may provide similar regenerative effects with fewer safety concerns. This review covers this progression, from the basic biology of cartilage to the search for effective treatments, and argues that standardising conditioned medium production is an important step toward its clinical use.

Keywords: osteoarthritis, cartilage, stem cells

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Cartilage Tissue

Cartilage is a firm, translucent, and resilient supportive connective tissue. Functionally, it provides a structural framework that serves as a template for subsequent bone deposition. Additionally, cartilage lines articular surfaces to absorb mechanical shock, diminish friction, and protect joints from mechanical damage. Cartilage tissue comprises resident cellular populations embedded within an extracellular matrix (ECM) (1).

The cellular components of cartilage tissue include chondrocytes, chondroblasts, and chondroclasts. Chondrocytes serve as the principal mature cells of the tissue. Chondroblasts, or cartilage-forming cells, are active during tissue development and regeneration, synthesising the intercellular matrix; these cells retain proliferative capacity and can differentiate into chondrocytes. Conversely, chondroclasts – or cartilage-resorbing cells – are modified multinucleated cells responsible for matrix degradation through lysosomal enzymatic activity (1,2).

The ECM is a cell-derived complex that fills the intercellular space surrounding chondrons. The chondron constitutes the primary structural unit of cartilage tissue, consisting of chondrocytes and their surrounding pericellular matrix. The matrix is composed primarily of hyaluronic acid, collagens, proteoglycans (e.g., chondroitin sulfate, keratan sulfate, aggrecan), glycosaminoglycans (GAGs), non-collagenous proteins, and water (1–3). This specific biochemical composition facilitates water retention, thereby conferring unique biomechanical properties upon the cartilage (2). Owing to the complete absence of blood vessels, lymphatic drainage, and neural innervation, cartilage exhibits an inherently limited intrinsic repair capacity (2).

Cartilage tissue is categorised into three main types: hyaline cartilage, elastic cartilage, and fibrocartilage. Hyaline cartilage exhibits distinct roles across developmental stages: during embryogenesis, it forms the primitive embryonic skeleton; during post-natal growth, it resides at the epiphyseal plate to mediate longitudinal bone elongation; and in the mature organism, it constitutes the majority of permanent cartilaginous structures, including the larynx, trachea, ribs, and nasal septum. Histologically, hyaline cartilage comprises an outer perichondrium layer, a sub-perichondrial zone housing chondrocytes residing in lacunae separated by abundant intercellular matrix, and deeper structural layers. Sub-perichondrial chondrocytes form several distinct layers of solitary, spindle-shaped cells, whereas chondrocytes in deeper zones assume a spherical morphology, increase in size, and aggregate into chondrons. Chondrocytes within a single chondron originate from a common progenitor (isogenous group) and are separated by a thin layer of intercellular matrix. Hyaline cartilage retains the capacity for remineralisation (2).

Table 1 A comparison of the types of cartilage – hyaline, elastic and fibrous (4).

Tissue type/characteristic	Hyaline cartilage	Elastic cartilage	Fibrous cartilage
presence of perichondrium	present	present	absent
cells	spindle-shaped chondrocytes in the lacunae, arranged in layers, separated by a large amount of intercellular substance, and larger, spherical chondrocytes, separated by a small amount of intercellular substance and grouped into chondrons	two- and three-cell chondrons separated by a small amount of intercellular substance	a few small, irregularly scattered, single- and two-cell chondrons
ECM	rich in type II collagen (COL2 α 1)	rich in elastin fibres	rich in type I collagen
location	embryonic skeleton, bone epiphysis and diaphysis, articular surfaces, cartilages of the larynx, trachea, bronchi, ribs, nasal septum	auricle, external auditory canal, Eustachian tube, epiglottis, cartilages of the larynx	intervertebral discs, pubic symphysis, menisci, sites of attachment of tendons and ligaments to bones

Elastic cartilage exhibits high compliance and flexibility, accommodating structural demands in locations such as the pinna, external auditory canal, Eustachian tube, epiglottis, and select laryngeal cartilages. It contains an extensive network of elastin fibres dispersed throughout the ECM, imparting both stiffness and elasticity, allowing rapid elastic recoil following mechanical deformation. Structurally, elastic cartilage consists of chondrons containing typically two to three regularly arranged chondrocytes surrounded by a sparse intercellular matrix. Elastic cartilage does not undergo mineralisation (4).

Fibrocartilage represents the most mechanically resistant subtype among cartilaginous tissues. It is localised primarily in anatomical regions subjected to high tensile stress, including intervertebral discs, the pubic symphysis, menisci, and tendinous or ligamentous insertion sites on bone. It is characterised by thick bundles of type I collagen fibres (COL1 α 1) arranged in a chevron pattern. The high collagen content relative to proteoglycan abundance provides exceptional tensile strength. Furthermore, fibrocartilage lacks a perichondrium and is continuously integrated with adjacent hyaline or elastic cartilage. Chondrons within this tissue are sparse and typically contain only one to two cells (1,4).

Cartilage Tissue Metabolism

Articular cartilage nutrition occurs exclusively via solute diffusion from the synovial fluid (SF), sustaining chondrocyte viability for ECM synthesis, maintenance, and repair. Under nutrient-deprived conditions, chondrocytes shift toward anaerobic metabolic pathways. Chondrocyte metabolic activity is regulated by local microenvironmental cues; specifically, pro-inflammatory cytokines such as interleukin-1 (IL-1) and tumour necrosis factor-alpha (TNF- α) exert both anabolic and catabolic downstream effects, mediating the synthesis and degradation of matrix macromolecules (5).

The metabolism of proteoglycans secreted into the ECM by chondrocytes is regulated by diverse growth factors and regulatory peptides, including insulin-like growth factor (IGF), transforming growth factor-beta 1 (TGF- β 1), IL-1, and TNF- α , via molecular mechanisms that remain incompletely understood (2).

Balanced ECM turnover – defined by the coordinated degradation and replacement of macromolecules – shields chondrocytes from biomechanical stress. The primary proteinases governing matrix turnover include matrix metalloproteinases (MMPs: collagenases, gelatinases, and stromelysins) and cathepsins (cathepsins B and D). Collagenases cleavage native collagen fibrils, whereas gelatinases hydrolyse denatured type II and IV α 1 collagen (COL4 α 1), fibronectin, elastin, and collagen types Va1 (COL5 α 1), VII α 1 (COL7 α 1), X α 1 (COL10 α 1), and XI α 1 (COL11 α 1). Stromelysins and cathepsins predominantly drive aggrecan degradation (6,7).

Organismal aging is a primary determinant of chondrocyte senescence and apoptosis, altering ECM composition, chondrocyte spatial organisation, and cellular responsiveness to extrinsic signals (8). With advancing age, chondrocyte density decreases within the superficial zone while increasing in deeper cartilage layers. Concurrently, matrix hydration declines, compromising tissue elasticity, compressive resistance, and reversible deformability. Aging also reduces the molecular size of proteoglycan aggregates within the ECM, impairing tissue permeability to essential solutes. Furthermore, an elevated keratan sulfate-to-chondroitin sulfate ratio disrupts ECM biochemical homeostasis (2).

Cellular senescence – initially defined by Leonard Hayflick in 1961 as an irreversible arrest of the cell cycle – readily affects chondrocytes (9,10). The term chondrosenescence specifically delineates age-dependent or trauma-induced cellular deterioration in cartilage (11). Notably, exposure to IL-1 β or serum supplementation induces chondrocyte senescence *in vitro* (11,12). Chondrosenescence driven by intrinsic factors (e.g., DNA replication errors) or extrinsic cell stress (13) is characterised by loss of differentiation potential alongside persistent pro-inflammatory mediator production, altered morphology and cell size, cell cycle arrest, dysregulated metabolic activity, heightened sensitivity to inflammatory and catabolic factors, blunted anabolic growth factor responsiveness, impaired repair capacity, and altered gene expression profiles (10,13,14).

The precise mechanisms driving senescence remain to be fully characterised but principally involve telomere shortening, double-stranded DNA damage, oxidative stress, and inflammatory cascades (15). In response to cellular stressors, premature cell cycle arrest is primarily executed via the p53/p21CIP1 and p16INK4A signalling pathways (14,16). Canonical markers of cellular senescence include components of these signalling cascades, senescence-associated beta-galactosidase (SA- β -gal) activity, formation of senescence-associated heterochromatic foci (SAHF), reduced lamin B1 expression, and accumulation of γ H2AX foci (11,16,17). Cells exhibiting a senescence-associated secretory phenotype (SASP) upregulated hyperplastic and inflammatory markers, including IL-6, IL-8, matrix metalloproteinase-13 (MMP-13), and vascular endothelial growth factor (VEGF) (11).

In addition to senescence, chondrocytes can undergo hypertrophy, a physiological process essential for endochondral ossification and longitudinal bone growth (11,18). Hypertrophic chondrocytes exhibit upregulated expression of type X collagen, Runt-related transcription factor 2 (RUNX2), and MMP-13 (19). Pathological hypertrophy contributes significantly to cartilage breakdown during osteoarthritis (OA) development, accompanied by the downregulation of articular markers, including type II collagen, aggrecan, and SRY-box transcription factor 9 (SOX9) (11,19,20). Hypertrophic chondrocytes ultimately undergo apoptosis or osteogenic transdifferentiation (11). Initiated primarily as a compensatory tissue repair response, the hypertrophic phenotype features dramatic cell volume expansion, reduced proliferative capacity, altered matrix secretion, enhanced remodelling, and matrix calcification (11,18). Signalling pathways governing hypertrophic changes include Wnt/ β -catenin, Indian hedgehog, parathyroid hormone-related peptide (PTHrP), TGF- β , fibroblast growth factors (FGF), SOX9, and bone morphogenetic proteins (BMPs) (19).

Ossification occurs predominantly during endochondral bone formation, initiated by hypertrophic chondrocyte apoptosis and subsequent matrix resorption by matrix metalloproteinases MMP-13 and MMP-9. This degradation allows the invasion of angiogenic and osteoplastic lineage cells (21). During ossification, chondrocytes initiate subchondral bone formation via hypertrophic differentiation (21,22). Chondrocytes participating in ossification secrete an ECM rich in type II, IX (COL9 α 1), and XI collagen, as well as proteoglycans such as aggrecan, alongside downregulated type I collagen expression (10).

In contrast to physiological ossification, cartilage calcification is a pathological process involving calcium crystal deposition within articular cartilage. Pathological calcification is linked to advanced age, metabolic disorders, genetic predisposition, and mechanical trauma, playing a central role in osteoarthritis pathogenesis (23–25). Although the regulatory pathways governing cartilage calcification are incompletely characterised, reactive oxygen species (ROS) and chondrocyte-derived apoptotic bodies serve as major inductive drivers (13,24).

Osteoarthritis

OA is characterised as a chronic inflammatory disorder affecting the joint and its surrounding tissues. Extensive research indicates that OA involves distinct metabolic, structural, and functional alterations localised within the articular cartilage, subchondral bone, synovial membrane, ligaments, and adjacent muscular tissue (26). Although its exact pathophysiology remains to be fully elucidated, the inflammatory cascade is predominantly mediated by an elevated release of cytokines and chemokines. These signalling molecules induce the synthesis of proteolytic enzymes, including matrix metalloproteinases, aggrecanases, and serine and cysteine proteases (26–28). Consequently, there is a downregulation of genes involved in chondrocyte differentiation, which adversely impacts cellular metabolism, regeneration, and proliferation, ultimately leading to apoptosis or hypertrophy (26,29). Key inflammatory mediators, specifically IL-1 β , IL-6, and TNF- α , secreted by damaged chondrocytes and intra-articular cells, further stimulate the production of secondary pro-inflammatory signalling molecules. This cascade disrupts homeostatic balance, shifting the cartilage dynamic toward catabolism over anabolism (26).

Articular cartilage lacks intrinsic innervation and vascularisation, so its capacity for self-repair is severely constrained. Furthermore, cartilage exhibits a complex, multi-layered architecture categorised into distinct subtypes. These subtypes vary in elasticity, governed by parameters such as cell density, extracellular matrix composition, and collagen fibre orientation, as well as in chondrocyte morphology and function (30). These structural and physiological features present significant hurdles to elucidating the underlying mechanisms of OA and hamper the development of effective therapeutic interventions.

Treatment of Osteoarthritis

Current therapeutic strategies for OA primarily focus on pain palliation resulting from cartilage degeneration. Pharmacological interventions, such as intra-articular injections, fail to restore tissue function, serving only to alleviate discomfort or delay disease progression. Advanced stages of OA typically necessitate total joint arthroplasty. Alternative surgical approaches, including bone marrow stimulation and tissue grafting, similarly fail to regenerate functional articular cartilage. Regenerative medicine strategies, namely autologous chondrocyte implantation (ACI) and its variants, offer promise for cartilage reconstruction, though these techniques present distinct clinical limitations (30–32).

Intra-articular administration utilises both natural compounds, such as ascorbic acid (33) and curcumin (34), and synthetic agents, including peroxiredoxin II (35) and rapamycin (36). Nevertheless, corticosteroids and hyaluronic acid (HA) remain the most widely administered agents (30). While many of these agents demonstrate efficacy at low concentrations, frequent high-dose administration risks chondrotoxicity. Furthermore, the efficacy of corticosteroid injections wanes over time (30), and clinical trials assessing HA injections show no significant therapeutic benefit over placebo in OA management (37).

Bone marrow stimulation techniques involve penetrating the subchondral bone to form channels, triggering the recruitment of multipotent bone marrow stem cells to the defect site to generate cartilage-like tissue (30,38). These procedures encompass microfracture, abrasion arthroplasty, and arthroscopic drilling (30,39). However, their application is restricted to small focal lesions and is ineffective for extensive defects or those extending deeper into the subchondral bone (39). Tissue grafting modalities, such as mosaicplasty and osteochondral allografting, entail harvesting tissue from non-weight-bearing sites for transplantation into the defect (30,39); both approaches carry a risk of graft rejection or donor-site morbidity (39).

Regenerative modalities include variations of ACI and matrix-induced autologous chondrocyte implantation (MACI). Both strategies involve harvesting patient-derived chondrocytes, combining them with a supportive matrix – such as a biodegradable collagen membrane in ACI or a 3D scaffold in MACI – and implanting the construct into the lesion (30,39). A major limitation of ACI and MACI is the requirement for a two-stage surgical procedure: an initial biopsy stage followed by implant placement (30). Moreover, these techniques carry a risk of fibrocartilage formation and are generally suitable only for small, localised defects (30,31).

Autologous platelet-rich plasma (PRP) injections represent another regenerative strategy, though the technique lacks approval from the Food and Drug Administration (FDA) for OA treatment (30). Recent studies suggest expanding regenerative approaches beyond autologous chondrocytes by using alternative cell types, including

mesenchymal stem/stromal cells (MSCs), embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), and cartilage-derived stem/progenitor cells (CSPCs). MSCs exhibit high accessibility, as they can be isolated from perinatal tissues (e.g., placenta, umbilical cord) or adult tissues (e.g., bone marrow, adipose tissue). MSCs feature robust proliferative and multilineage differentiation potential, anti-inflammatory properties, and immunomodulatory activity. However, cell transplantation strategies risk losing the endogenous repair capacity or alter natural tissue architecture (30,39–41). ESCs and iPSCs offer unlimited proliferation and pluripotency across all three germ layers, yet their translational utility remains constrained by ethical concerns, risks of immune rejection, teratoma formation at the injection site, and low differentiation efficiency (30,42,43). CSPCs display high proliferative capacity, chondrogenic differentiation potential, and stemness marker expression, but their clinical translational utility remains restricted due to uncharacterised therapeutic profiles (30).

Cell-free therapies utilising conditioned medium (CM) have emerged as a notable derivative of cell-based paradigms. "Conditioned medium" refers to the supernate harvested from *in vitro* cell cultures, enriched with secretome components including cytokines, growth factors, extracellular matrix proteins, matrix remodelling factors, and extracellular vesicles (44). The principal mechanism by which stem cells facilitate tissue repair is their paracrine activity; the secretion of trophic factors limits tissue damage, prevents ongoing degeneration, and enhances repair pathways (45). A key advantage of CM over cell transplantation is that it delivers only the secretome, harnessing the therapeutic mechanisms of stem cells while bypassing the risks associated with live cell transplantation.

Because distinct cell types possess unique properties and secretome profiles, the cell source must be aligned with the target pathology (46). CM has been derived from various stem cell sources, including bone marrow MSCs (BM-MSCs), adipose-derived MSCs (AD-MSCs), placental cells, umbilical cord cells, umbilical cord blood cells, amniotic cells, dental pulp cells (such as periodontal ligament stem cells (PDLSCs) and stem cells from human exfoliated deciduous teeth (SHED)), and Wharton's jelly MSCs (WJ-MSCs) (46–48). However, literature evaluating iPSC-derived CM in OA therapy remains sparse.

By eliminating intact cells from the biological therapeutic, CM minimises the risk of graft-versus-host reaction and adverse recipient immune responses. The procurement process for CM is generally faster, more cost-effective, and avoids donor-recipient matching requirements, while delivery is less invasive than cellular transplantation. Crucially, CM mitigates tumourigenic risks – a major safety concern in cell therapy. Recent findings indicate that CM may be suitable for treating larger osteochondral defects associated with OA (49–51).

Despite its advantages, potential limitations of CM include batch-to-batch variability and incompletely characterised composition. Standardised production protocols have not yet been established, resulting in variability across research laboratories (52). These discrepancies stem from differences in basal media composition, parental cell source, and *in vitro* culture parameters (46,52,53). Systematic analysis and standardisations are required to fully elucidate the mechanism of action of CM, overcome production variability, and enable clinical translation.

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