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A new perspective on the mechanism exploration and treatment of osteoarthritis

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Osteoarthritis (OA) has long been defined as the progressive and irreversible loss of articular cartilage, a tissue known for its poor intrinsic regenerative capacity. The currently popular treatment strategies are palliative care or joint prosthesis replacement in end-stage diseases. However, the discovery of the resident population of cartilage progenitor cells (CPCs) within adult articular cartilage fundamentally challenges the long-held view that adult articular cartilage has limited intrinsic repair capacity. These cells possess clonogenicity, multipotency, and chondrogenic differentiation ability, and are potential repositories for tissue maintenance and repair. This view holds that the failure of OA cartilage is not merely a failure of matrix integrity, but more importantly, it is a failure of the endogenous progenitor cell system. In addition, mechanical stimulation and metabolic factors are both crucial for cartilage regeneration and repair as well as the determination of the fate of progenitor cells. With the rise of nucleic acid therapy, we can envision that gene therapy and stem/progenitor cell therapy will shift their therapeutic goals from slowing down degeneration to promoting true regeneration.

RESEARCH PARADIGM CHANGE CAUSED BY CHONDROPROGENITOR CELL RESEARCH BOOM

For decades, osteoarthritis has been regarded as a passive "wear and tear" process. Over time, mechanical stress has inevitably eroded the structure of articular cartilage.[1] The traditional view holds that chondrocytes are the sole cells of cartilage and are passive victims of environmental deterioration. The limited anabolic response observed in osteoarthritis (OA) chondrocytes was seen as a feeble and ultimately futile attempt to compensate for overwhelming destruction. This understanding logically led to therapeutic strategies focused on dampening inflammation, approaches that have failed to demonstrate robust disease modification in clinical trials.

The identification of cartilage stem/progenitor cells—often referred to as cartilage progenitor cells (CPCs)—has renewed interest in the concept that adult articular cartilage may harbor a limited endogenous reparative cell pool.[2] CPC-like cells have been reported to be enriched in the superficial zone and associated niches, supporting the idea that cartilage possesses a dedicated, albeit restricted, mechanism for homeostasis and repair. The central argument of this new perspective is that the progress of OA is not only driven by chondrocyte hypertrophy and extracellular matrix destruction, but also by functional impairment of the CPCs population (Figure 1). In early OA, CPCs proliferate and attempt to mount a repair response, often observed as cluster formation. However, in established and advanced disease, this reparative attempt is aborted. CPCs become senescent, undergo aberrant differentiation, or are suppressed by a hostile disease microenvironment. Therefore, the core pathology of OA can be reinterpreted as a failure of progenitor cell-mediated homeostasis. Understanding and correcting this failure in treatment may be the next frontier in the search for a disease-modifying osteoarthritis drug (DMOAD).

DEFINING CPCS AND THE DETERMINANTS OF THEIR FATE IN OA

Definition and nomenclature

The precise definition and identification of CPCs within the field remain controversial. Unlike hematopoietic stem cells, chondroprogenitor cells lack a single, universally agreed-upon marker within the field. This absence has led to a diverse and often confusing nomenclature, including terms such as "cartilage stem/progenitor cells", "mesenchymal stem cell (MSC)-like cells from cartilage," and "superficial zone cells". A practical way forward is to define CPCs using functional criteria (clonogenicity, self-renewal, and in vivo lineage behavior) complemented by marker panels.[3]

Localization, candidate markers, and relationship to SSCs

Recent studies have identified Procr$^+$ CPCs, which also constitute a PRG4$^+$ cell subset.[3] Their specific localization in the superficial zone and other niches is not coincidental—these niches are believed to provide unique biochemical and biomechanical microenvironments that maintain their progenitor cell state.

To broaden this perspective, CPCs can be discussed within the emerging skeletal stem/progenitor framework, in which operational criteria—self-renewal, clonal output, and in vivo lineage behavior—have enabled hierarchical models that are reproducible across multiple skeletal compartments. For instance, human skeletal stem/progenitor populations defined by combinatorial surface-marker panels have been isolated from distinct anatomical sites and functionally validated, supporting a conserved progenitor logic that extends beyond a single tissue niche. Complementary work on periosteal stem/progenitor populations further illustrates that skeletal progenitors are anatomically specialized yet share common functional principles, particularly in injury-responsive contexts. Framing CPCs in this broader context helps interpret their heterogeneity and highlights why developmental programs and niche-regulated signaling modules can be reutilized in the postnatal joint to influence CPC fate. Dysregulation of these CPC-governing programs is increasingly implicated in OA progression.

Extrinsic cues regulating CPC fate in OA

Piezo1 and GLP-1 signaling. Piezo1 is a mechanosensitive, non-selective cation channel on the plasma membrane. In articular cartilage, published studies report context-dependent roles of Piezo1: inflammatory or overload-like stimuli can enhance Piezo1-mediated Ca^{2+} entry and catabolic responses in differentiated chondrocytes, whereas in Procr$^+$ CPCs Piezo1 has been proposed to support mechanotransduction required for progenitor activation and repair.[3] Given these apparently divergent observations, the function of Piezo1 in CPCs should be interpreted cautiously and discussed alongside the broader cartilage literature. Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted by intestinal L cells in response to nutrient intake and signals through the GLP-1 receptor (GLP1R). In OA, current evidence primarily supports an indirect role of GLP1R signaling by modulating the joint microenvironment—reducing synovial inflammation and dampening catabolic responses in mature joint-resident cells (e.g., chondrocytes and macrophages), where GLP1R expression has been demonstrated. However, whether GLP1R signaling directly regulates CPCs fate remains unclear and should be addressed by future studies that map GLP1R expression and functional responses specifically within CPCs subsets.[4]

The TGF-β/BMP superfamily. In CPCs, this axis governs the balance between stable chondrogenic differentiation and hypertrophic drift. OA-associated dysregulation can bias progenitor fate toward hypertrophy and aberrant matrix remodeling, underscoring the need for context- and timing-dependent modulation rather than uniform pathway activation.[5]

Wnt/β-catenin signaling. Wnt activity must be tightly tuned: basal signal-

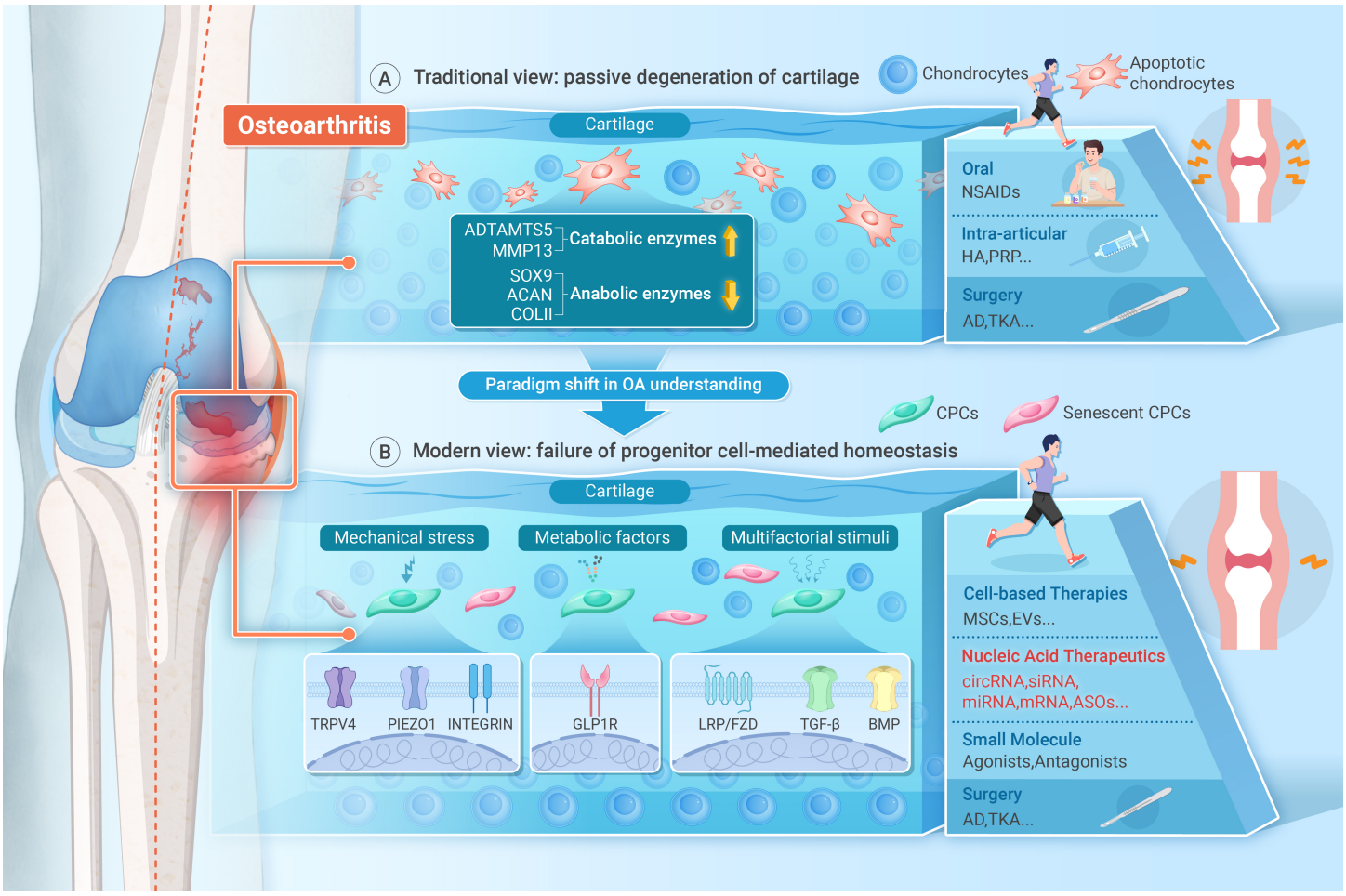

Figure 1. Conceptual illustration of the paradigm shift in osteoarthritis research From the traditional "wear-and-tear" model emphasizing passive matrix degradation and chondrocyte loss, to a new model highlighting CPCs dysfunction as the central driver of impaired regeneration and disease progression. NSAIDs, Nonsteroidal Anti-Inflammatory Drugs; HA, Hyaluronic Acid; PRP, Platelet-Rich Plasma; AD, Arthroscopic debridement; TKA, Total Knee Arthroplasty; MSCs, Mesenchymal Stem Cells; EVs, extracellular vesicles; circRNA, Circular RNA; siRNA, Small Interfering RNA; miRNA, MicroRNA; mRNA, Messenger RNA; ASOs, Antisense Oligonucleotides. Not to scale.

ing can support progenitor maintenance, whereas sustained activation in OA is linked to impaired chondrogenic maturation and a shift toward non-hyaline repair outcomes (e.g., fibrocartilaginous or hypertrophic programs). Thus, therapeutic logic should focus on restoring an appropriate Wnt "set point" in progenitor compartments.[6]

Intrinsic programs: Epigenetic state and senescence

Beyond extracellular signals, the intrinsic state of CPCs is a major determinant of their regenerative capacity. Epigenetic regulation (DNA methylation, histone modifications, and non-coding RNAs) shapes differentiation competence, while cellular senescence and the senescence-associated secretory phenotype (SASP) can create a pro-inflammatory, matrix-degrading milieu that suppresses neighboring progenitor function and broadly impairs endogenous repair in aging and OA.[7]

FROM PATHOPHYSIOLOGICAL INSIGHT TO CLINICAL TRANSLATION

Understanding OA as a disorder of CPCs dysfunction provides a clear roadmap for novel therapeutic strategies. The goal is no longer just to stop breakdown but to actively promote regeneration by rescuing, re-educating, and re-engaging the endogenous progenitor population.

From this perspective, three CPC-guided avenues can be prioritized: ①**CPC state modulators:** Best suited when CPCs are present but exhibit misspecified fate decisions (e.g., inadequate chondrogenic maturation or hypertrophic/fibrocartilaginous drift). The rationale is to use short, stage- and dose-controlled intra-articular modulation of Wnt or TGF-β/BMP set points to separate progenitor expansion from subsequent differentiation. This option is most appropriate for disease stages where a reparative CPC pool is still detectable and the main barrier is instructional signaling, rather than profound cell loss. ②**Local RNA-based reprogramming:** Preferred when the dominant limitation is CPC-intrinsic dysfunction (senescence/SASP, impaired mechanotransduction, or maladaptive transcriptional/epigenetic programs) that is unlikely to be corrected by pathway tuning alone. The indication is OA phenotypes with evidence of inflammatory stress and durable gene-network dysregulation, where joint-retained nucleic-acid modalities can provide sustained, target-specific correction. For example, a chemically stabilized siRNA strategy achieved preferential delivery to inflamed joints with sustained gene silencing and improved outcomes in preclinical arthritis/OA models.[8] Delivery advances and intra-articular bioactive platforms further support the practicality of localized nucleic-acid interventions for OA.[9] ③**Stem cell-based approaches:** Most appropriate when the key barrier is a non-permissive microenvironment (persistent inflammation, catabolic mediators, matrix fragments) that suppresses CPC survival and function. Here, stem cell–derived EVs and biomaterial-assisted delivery can act as CPC-enabling tools by reconditioning the niche, dampening inflammatory stress, and providing regenerative cues, particularly when direct reprogramming or single-pathway modulation is insufficient.[10]

Given the multifactorial dysregulation, it is unlikely that a single-target approach will be sufficient. The most successful strategies will likely be combinatorial. For example, a treatment regimen might involve an initial step of senolytic clearance to remove negative influences, followed by the delivery of a growth factor cocktail within a supportive scaffold to actively guide the now-competent population of CPCs through a coordinated repair process.

DISCUSSION AND CONCLUSION

The path to clinical translation is fraught with challenges. The heterogeneity of the CPCs population necessitates better tools for their identification and

isolation. The risk of off-target differentiation, such as ossification or the formation of fibrocartilage, must be meticulously managed. Delivering therapeutics specifically to this cell population within the dense, avascular cartilage matrix remains a significant bioengineering hurdle, and will likely require tailored delivery platforms—such as hydrogel-based carriers that improve local retention and controlled release, or minimally invasive injection approaches (including microfluidic-assisted injection systems) designed to enhance penetration and spatial precision within cartilage. Furthermore, long-term safety studies will be crucial to ensure that manipulating progenitor cell fate does not lead to unforeseen consequences, such as neoplastic transformation.

While MSCs have been explored for OA for decades, their clinical impact has often been limited by poor persistence and uncertain tissue specificity. Viewed through a CPC-centered framework, MSC-based interventions may be most valuable not as cell replacement, but as niche-modulating tools that deliver transient trophic/immune cues (including via secretome/EVs) to protect, recruit, and re-engage endogenous CPCs and thereby restore intrinsic repair capacity. This shift—from treating cartilage as an inert matrix to targeting dysfunctional cellular repair units—reframes OA as a potentially correctable failure of joint regenerative programs and provides a more mechanistically grounded roadmap for therapeutic development. Ultimately, therapies that combine microenvironmental reconditioning with CPC-targeted activation may offer more durable benefits for degenerative joint disease.

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AUTHOR CONTRIBUTIONS

All authors contributed to and approved the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

DATA AND CODE AVAILABILITY

No new data were created or analyzed in this study.