Review

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The misinterpreted boundary

Clarifying the unique attributes of the cartilaginous endplate and its central mechanism in intervertebral disc degeneration

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Abstract: The intervertebral disc (IVD) is a complex structure vital for spinal function, whose degeneration is a leading cause of low back pain. While research has traditionally focused on the nucleus pulposus (NP) and annulus fibrosus (AF), the cartilaginous endplate (CEP)—the critical interface between the disc and vertebral body—has been historically underappreciated and often anatomically conflated with the adjacent bony endplate (BEP). This review aims to systematically synthesize current knowledge to clarify the unique attributes of the CEP and establish its role as the primary initiator of the IVD degenerative cascade. We first elucidate the fundamental biology of the CEP, distinguishing its distinct histological identity and dual "mechanical and nutritional" functions, which are essential for disc homeostasis. Subsequently, we detail the morphological progression and functional consequences of CEP degeneration, emphasizing its strong clinical relevance to discogenic pain and treatment outcomes. A core section critically examines the mechanisms of degeneration, focusing on the traditional "nutrient deprivation hypothesis" linked to reduced CEP permeability and a newer perspective highlighting the paramount importance of CEP–BEP interfacial integrity as a potential initiator of pathological cascades. We then evaluate the characteristics and limitations of various animal models used in CEP research, providing guidance for model selection based on specific scientific questions. Furthermore, we summarize recent advances in the molecular and cellular mechanisms driving CEP degeneration, including dysregulated matrix metabolism, aberrant mechanotransduction, oxidative stress, and epigenetic regulation. In conclusion, this review positions the CEP not as a passive structure but as an active hub whose health dictates IVD fate. Recognizing CEP degeneration as a pivotal driver offers significant translational relevance, shifting the clinical focus toward early-stage diagnosis and disease-modifying therapeutic strategies. Future interventions targeting CEP matrix health and interfacial integrity hold the potential to halt or reverse disc degeneration at its source, providing a paradigm shift in the management of chronic low back pain.

Abbreviations: ADAMTS = a disintegrin and metallopeptidase with thrombospondin motifs, AF = annulus fibrosus, BEP = bony endplate, CEP = cartilaginous endplate, COL10A1 = collagen type X alpha 1 chain, ECM = extracellular matrix, EZH2 = enhancer of zeste 2 polycomb repressive complex 2 subunit, GAG = glycosaminoglycan, IDD = intervertebral disc degeneration, IVD = intervertebral disc, MGP = matrix Gla protein, MMP = matrix metallopeptidase, mTOR = mechanistic target of rapamycin, NF-κB = nuclear factor kappa B, NP = nucleus pulposus, Nrf2 = nuclear factor erythroid 2-related factor 2, Piezo1 = piezo-type mechanosensitive ion channel component 1, scRNA-seq = single-cell RNA sequencing, SOX9 = SRY-box transcription factor 9, VEGF = vascular endothelial growth factor, YAP = yes-associated protein.

Keywords: animal models, calcification, cartilaginous endplate, intervertebral disc degeneration, low back pain, mechanotransduction, nutrient transport

1. Introduction

The intervertebral disc (IVD) is a core structure responsible for spinal mechanical support and mobility, whose integrity is fundamental to spinal health. Classical

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anatomy describes the IVD as a tripartite complex: the central nucleus pulposus (NP), rich in proteoglycans and water; the peripheral annulus fibrosus (AF), composed of concentrically arranged collagen fibers; and the cartilaginous endplate (CEP), which caps the vertebral body's cortical endplate superiorly and inferiorly, directly interfacing with the NP and the inner AF. For a long time, research focus has predominantly centered on NP degeneration and AF rupture, while the significance of the CEP—a critical interface between the disc and vertebral body—has often been underestimated or neglected.[1]

The CEP is a thin yet dense layer of hyaline cartilage. It not only provides crucial craniocaudal mechanical anchoring for the innermost AF and the NP matrix, preventing disc tissue from protruding into the vertebral body, but also serves as the sole lifeline for nutrient influx and metabolic waste efflux in this avascular tissue. This unique dual "mechanical and nutritional" function means the health status of the CEP directly dictates the internal homeostasis of the IVD. However, the CEP faces significant conceptual ambiguity in both research and clinical practice: anatomically, it is often conflated with the adjacent bony endplate (BEP) on the vertebral side under the umbrella term "vertebral endplate", obscuring its distinct histological identity and function; pathologically, early CEP degeneration (e.g., calcification and micro-fissures) is frequently viewed as a passive concomitant rather than a potential initiating factor driving overall disc degeneration.[2]

Thus, a systematic synthesis of knowledge regarding the CEP is of paramount importance for a deeper understanding of the pathological mechanisms underlying intervertebral disc degeneration (IDD) and for developing novel therapeutic strategies. This review aims to: first, elucidate the anatomical definition, developmental biological basis, and core physiological functions of the CEP; second, investigate in depth the morphological manifestations and functional consequences of CEP degeneration and its association with clinical conditions such as low back pain; subsequently, focus on the central aspects of "porosity and interfacial integrity", analyzing their regulatory role in nutrient transport and the impact of degeneration; then, critically appraise the characteristics and limitations of different animal models used in CEP research; and finally, summarize recent advances in the molecular and cellular mechanisms of CEP degeneration. Through this comprehensive synthesis, we aim to elevate the recognition of the CEP's pivotal role in IVD homeostasis and disease and to provide a reference for future research directions. Notably, despite recent progress, significant challenges persist, particularly the lack of noninvasive, CEP-specific clinical biomarkers and the anatomical limitations of current animal models. Addressing these hurdles through multi-omics integration and the development of targeted mechanobiological interventions represents the next critical frontier for shifting from symptomatic relief to true disease-modifying therapies for the IVD.

2. Fundamental biology of the CEP

2.1. Anatomical and histological definition: a unique and often-confused interface

The CEP is a layer of hyaline-like cartilage tissue situated between the BEP and the IVD components—the NP and the inner AF. While structurally and functionally intricately integrated with the BEP, often collectively termed the "vertebral endplate," this nomenclature frequently leads to confusion in the literature, where "vertebral endplate" is sometimes mistakenly equated with the BEP alone. A clear distinction from histogenetic and functional perspectives is crucial: the BEP is a dense, porous cortical bone layer on the surface of the vertebral cancellous bone, primarily providing mechanical support and harboring vascular channels from the vertebral marrow. In contrast, the CEP is an avascular cartilage layer (approximately 0.1–1 mm thick), composed of type II collagen, proteoglycans, and water, which directly contacts the disc tissue. Together, they form a composite structure at the disc–vertebra interface, but the CEP is the direct functional unit mediating nutrient exchange and interfacial mechanical transmission.

Traditionally, the CEP has often been analogized to articular cartilage (AC). However, recent research has revealed its distinctiveness. A systematic comparative study by Lakstins et al.[3] demonstrated that the CEP differs significantly from AC in cell morphology (elongated, spindle-shaped cells aligned along collagen fibers), matrix composition (significantly lower glycosaminoglycan [GAG] content than NP, with proteoglycans enriched pericellularly), and gene expression profiles. Critically, the CEP exhibits high expression of collagen type X (COLX), a marker typically associated with hypertrophic growth plate cartilage but expressed at very low levels in mature AC. Overall, the CEP shows greater structural and phenotypic similarity to the AF, particularly its inner layers, than to AC. Therefore, the CEP should be defined as a specialized cartilaginous tissue with a unique matrix composition and cellular phenotype, constituting an integral and inseparable component of the IVD (Table 1).[3]

Recent advancements in single-cell transcriptomics have refined the molecular boundary of the CEP. Beyond its collagenous framework, the CEP is defined by a unique transcriptomic signature. Unlike AC, the CEP maintains constitutively high expression of collagen type X alpha 1 chain (COL10A1) and matrix Gla protein (MGP). Furthermore, single-cell RNA sequencing (scRNA-seq) analysis of human endplates has identified 9 distinct cellular clusters, including chondroblasts (CB), which express chondrogenic markers like chondromodulin (CNMD), lumican (LUM), and decorin (DCN). These molecular signatures provide a robust toolkit for distinguishing the CEP from its surrounding compartments.

2.2. Development and age-related changes: the physiological "switch" and pathological divergence

The CEP shares a common ontogeny with the IVD, originating from the embryonic axial mesoderm. Regulated by

Table 1

Comparative characteristics of the CEP, AC, and iAF.

Feature	CEP	AC	iAF
Primary function	Mechanical anchorage; nutrient diffusion	Load bearing, shock absorption, and lubrication	Resists tensile and hoop stresses; contains NP
Cell morphology	Elongated, spindle-shaped, aligned along fibers	Rounded/polygonal, often in chondrons	Highly elongated, fibroblast-like
Dominant collagen type	Type II (major), type X (high expression)	Type II (major), VI, IX, XI	Type I (major), type II
Proteoglycan/GAG content	Moderate; lower than NP; pericellular enrichment	High (particularly in the superficial zone)	Low
Vascular/neural innervation (healthy adult)	Avascular; aneural	Avascular; aneural	Vascular/neural ingrowth in outer layers only
Key molecular markers	COL10A1^{high}, MGP, CNMD, CHAD	COL2A1^{high}, ACAN^{high}, PRG4	COL1A1^{high}, DCN
Mechanical property	Relatively stiff; acts as a diffusion barrier	High compressive stiffness and resilience	High tensile strength and toughness
Developmental origin	Axial mesoderm (with disc)	Limb bud mesenchyme	Axial mesoderm (with disc)

This table highlights the unique hybrid phenotype of the CEP, sharing some characteristics with both AC (e.g., type II collagen base) and iAF (e.g., elongated cell morphology), while being distinctly defined by features such as high type X collagen expression and its specialized role as a biomechanical and metabolic interface.AC = articular cartilage, CEP = cartilaginous endplate, CNMD = chondromodulin, DCN = decorin, GAG = glycosaminoglycan, iAF = inner annulus fibrosus, NP = nucleus pulposus.

the coordinated expression of *paired box gene 1* (*Pax1*) and *paired box gene 9* (*Pax9*), sclerotome cells encapsulate the notochord to form the primitive disc structure. While the notochordal cells aggregate to form the NP, the mesenchyme connected to the superior and inferior surfaces of the vertebral cartilage anlagen differentiates into the permanent CEP, establishing the early osteocartilaginous interface.[4]

2.2.1. The molecular switch: mechanisms of physiological devascularization. Postnatally, the CEP undergoes a critical functional transformation, transitioning from a primary site of longitudinal vertebral growth to a specialized metabolic interface. In early childhood, the CEP is relatively thick and characterized by abundant vascular channels originating from the vertebral bone marrow, serving a role analogous to the epiphyseal growth plate.

As skeletal maturity approaches, a pivotal "switch mechanism" is initiated to render the CEP avascular. This physiological devascularization is driven by a sophisticated interplay between biochemical signaling and structural remodeling. Chondrocytes within the maturing CEP significantly upregulate potent antiangiogenic factors, most notably Chondromodulin-I (Chm-I), which antagonizes proangiogenic signals such as vascular endothelial growth factor (VEGF) to inhibit endothelial proliferation. Concurrently, the matrix undergoes a programmed hypertrophic-like shift, marked by the secretion of COL10A1 and MGP. This leads to the mineralization of the pericellular matrix, creating a dense, sheet-like barrier that mechanically occludes preexisting vascular channels. By early adulthood, this switch specializes the CEP as a mature, avascular, semi-permeable membrane—establishing the "lifeline" upon which the disc relies for passive nutrient diffusion.[5–7]

2.2.2. From geometric remodeling to pathological profiling. During aging, the CEP undergoes significant geometric changes. High-resolution magnetic resonance imaging (MRI) studies, such as those by DeLucca et al.,[5] have quantified age-related decreases in human lumbar CEP thickness and area, often exhibiting spatial heterogeneity (e.g., central thinning). However, a critical observation in clinical research is the dissociation between gross geometry and the severity of IDD. Because morphological thinning often represents a physiological adaptation rather than a disease state, geometric metrics are poor surrogates for the functional status of the disc.

Consequently, clinical and mechanistic evaluation must shift from mere "geometric assessment" to "pathological profiling". True pathological degeneration is characterized by aberrant neovascularization and chronic inflammation rather than macroscopic thinning. Recent scRNA-seq landscapes[8] have revealed that the hallmarks of a degenerating endplate are the recruitment of immune cell clusters (e.g., macrophages [MA]) and the transcriptomic divergence of chondrocytes. High-resolution profiling identifies specific subpopulations, such as CB—uniquely marked by CNMD and DCN—and reveals a shift toward an inflammatory trajectory (fate 1). This pathological profiling—integrating revascularization density, infiltrating immune cell signatures, and the loss of homeostatic molecular markers (e.g., CHAD and MGP)—provides a significantly more robust framework for assessing IDD severity and discogenic pain than traditional morphological dimensions[9,10] (Table 2).

2.3. Core physiological functions: mechanical integration and the lifeline

As the sole direct contact interface between the IVD and the vertebral body, the CEP fulfills two indispensable and interdependent physiological roles: maintaining mechanical integrity and regulating nutrient and metabolic exchange. These dual functions work in concert to ensure the internal homeostasis of the disc.

2.3.1. Mechanical function: mechanical anchoring and stress distribution. The primary mechanical role of the CEP is to serve as a mechanical anchor and barrier. Its collagen fiber network interweaves and is continuous with the fibers of the inner AF, providing a robust craniocaudal

Table 2

Key developmental and age-related stages of the CEP.

Life stage	Key morphological features	Vascular status	Primary function
Embryonic/neonatal	Relatively thick; contains abundant vascular channels	Vascularized	Serves as a growth plate for vertebral body elongation; primary nutrient source for the disc
Childhood (before about 10 years)	Gradual occlusion and filling of vascular channels with ECM	Devascularization	Transitional phase; growth function declines as it transforms into a diffusion barrier
Healthy adulthood	Thin, dense layer of avascular hyaline cartilage; integrated with BEP	Avascular	Mature mechanical barrier and semi-permeable membrane for nutrient/waste exchange
Degeneration/injury	Micro-fissures, calcification, ossification, and structural defects	Pathological revascularization	Loss of barrier function; conduit for aberrant vascular and neural ingrowth, inflammation, and pain

The dynamic transition from a vascularized growth plate to an avascular diffusion barrier, and subsequent pathological revascularization upon injury, is a hallmark of CEP biology and fundamentally distinguishes it from AC.

mechanical attachment point for the innermost AF and the NP matrix. This anchorage effectively "locks" the disc securely between adjacent vertebral bodies. This anchoring function is crucial for resisting shear and tensile forces generated during spinal flexion, torsion, and compression. Concurrently, acting as a resilient cartilaginous barrier, the CEP effectively prevents the high hydraulic pressure within the NP from causing bulging or protrusion of disc tissue into the relatively porous vertebral cancellous bone under axial compressive loads.

Furthermore, the CEP serves as a key stress distributor for spinal axial loads. When load is transmitted through the vertebral body, the relatively stiff and porous BEP first contacts the pressure. The CEP subsequently utilizes its water- and proteoglycan-rich viscoelastic matrix to buffer and redistribute this stress, facilitating its more uniform transfer to the underlying NP and AF. This buffering effect attenuates stress concentrations, thereby protecting both the vertebral bone and the disc matrix from damage. Consequently, the mechanical integrity of the CEP is directly linked to the biomechanical performance of the entire spinal motion segment.

2.3.2. Nutritional and metabolic function: the lifeline of an avascular tissue. The IVD is the largest avascular tissue in the human body, and the survival of its resident cells is entirely dependent on solute diffusion from surrounding tissues. The CEP constitutes the most critical link in this core pathway for nutrient influx and waste efflux.

The exchange of nutrients (e.g., glucose and oxygen) and metabolic wastes (e.g., lactate) occurs primarily via passive diffusion. This process relies on concentration gradients: nutrients released from the rich capillary network within the vertebral bone marrow cavity must first traverse the porous BEP and then pass through the extracellular matrix (ECM) of the CEP to reach the cells of the NP and AF. Conversely, metabolic wastes produced by the cells exit along the reverse pathway. The composition of the CEP matrix—specifically, the packing density of collagen fibers, and the content and charge of proteoglycans—directly determines its diffusive permeability. Functioning akin to a "biological filter", it regulates the transport rates of various solutes.

Notably, the "source" of the nutrient supply is located within the marrow contact channels (also termed endplate pores) of the BEP, which contain vascular buds. Once solutes diffuse from these vessels, the permeability of the CEP becomes the primary limiting factor for their efficient diffusion into the deeper regions of the disc. Therefore, the health status of the CEP—specifically, whether it has undergone calcification or matrix degeneration—directly determines whether cells in the disc's core region (NP) receive adequate nutrition to sustain matrix synthesis and avoid the acidic environment caused by lactate accumulation. The latter can accelerate cell apoptosis and matrix degradation. This function elevates the CEP from a mere mechanical structure to a lifeline crucial for maintaining the metabolic homeostasis of the IVD.

3. Degeneration of the CEP: manifestations, implications, and clinical relevance

IDD is a multifactorial and progressive process, in which degeneration of the CEP plays a role that is not merely passive but potentially initiatory and driving. CEP degeneration represents a continuum of concurrent morphological and functional deterioration.

3.1. Morphological progression of degeneration: from microscale disruption to structural loss

CEP degeneration begins with biochemical and structural imbalances at the microscopic level. Early hallmarks include degradation of the ECM (proteoglycan loss, disorganization of the collagen network), chondrocyte apoptosis or necrosis, and the formation of micro-fissures. These micro-fissures may occur within the CEP itself and, more critically, at the interface between the CEP and the underlying BEP. Recent ultrastructural studies have revealed that this interface commonly contains micron-scale gaps connected by fragile "adhesive bridges", the width of which increases with worsening degeneration, creating a weak point in structural integrity.[11]

Subsequently, degeneration progresses into a phase marked by pathological calcification and ossification. Chondrocytes transition toward a hypertrophic-like phenotype, secreting type X collagen and promoting matrix

mineralization. Vascular and mesenchymal cells from the vertebral body can aberrantly invade through the compromised interface, triggering ectopic bone formation. This process leads to thickening and hardening of the CEP, with a gradual loss of its inherent hyaline cartilage characteristics. Ultimately, in advanced stages of degeneration, the cartilaginous tissue of the CEP may be completely replaced by bone tissue, resulting in the functional effacement of this critical interface.

These microscopic morphological progressions serve as the structural substrate for radiological hallmarks observed in clinical practice. Specifically, the pathological calcification and increased mineral density of the CEP are closely associated with the development of Modic changes—signal alterations in the vertebral endplates and adjacent bone marrow visible on MRI. While Modic type I changes represent an acute inflammatory/edematous phase, Modic type II (fatty replacement) and type III (sclerosis) changes are particularly indicative of chronic CEP deterioration.

The structural separation and micro-fissures at the CEP–BEP interface, as highlighted by recent ultrastructural studies, may directly underlie the signal voids and irregularities seen on high-resolution MRI. By linking these microscopic defects to established clinical classifications, the CEP is repositioned not just as a pathological site, but as a primary radiological biomarker for assessing the severity and progression of IDD.

3.2. Functional consequences of degeneration

Morphological disruption directly leads to the failure of the CEP's two core functions, thereby triggering a cascade of disc degeneration.

3.2.1. Impairment of nutrient transport. Calcification, thickening, and matrix degeneration of the CEP significantly reduce its permeability, impeding the diffusion of nutrients toward the disc center and the egress of metabolic wastes. This traps the NP region in a vicious cycle of "nutrient deprivation and acidosis".[12] Cells, suffering from energy insufficiency, exhibit reduced anabolic activity and become unable to maintain the turnover of matrix components like proteoglycans. Concurrently, the acidic environment further accelerates the activity of matrix-degrading enzymes and promotes cell apoptosis. Therefore, CEP degeneration is widely regarded as a primary contributor to the core biochemical alterations in disc degeneration, such as NP dehydration and proteoglycan loss.

3.2.2. Loss of mechanical integrity. The mechanical properties of a degenerated CEP are severely compromised. Calcification and sclerosis increase its brittleness and decrease its elasticity, diminishing its ability to buffer stress. More critically, the propagation of micro-fissures and the separation of the CEP–BEP interface disrupt its mechanical anchoring function. This leads to two major consequences: first, the endplate itself becomes prone to fracture or detachment; second, the high-pressure NP tissue can more easily protrude through defects into the vertebral cancellous bone, forming Schmorl's nodes. Both scenarios further destabilize the biomechanics of the spinal motion segment and can incite inflammation and pain.[13]

3.3. Clinical relevance of degeneration

Degeneration of the CEP is closely associated with the clinical manifestations of various spinal disorders. Imaging and pathological studies confirm the following.

3.3.1. Strong association with IDD. Alterations in the lumbar vertebral endplate, which includes the CEP, such as Modic changes and osteophyte formation, demonstrate a significant positive correlation with the severity of disc degeneration. Measurements of endplate morphology, endplate angle, for instance, can serve as auxiliary indicators for assessing IDD.[14]

3.3.2. As a source of pain. Degenerated and defective endplate regions are often accompanied by aberrant ingrowth of nerve endings and localized inflammatory responses. Furthermore, the micromotion and inflammation associated with endplate fractures or during the formation of Schmorl's nodes are considered important biomechanical and biochemical sources of discogenic low back pain.

3.3.3. Impact on treatment prognosis. Severe calcification and sclerosis of the CEP, due to their role in impeding nutrient diffusion, are recognized as a key limiting factor affecting the efficacy of intradiscal biological therapies, such as cell transplantation or growth factor injection.[15]

In summary, CEP degeneration is far from an isolated local phenomenon. Rather, by compromising both nutrient supply and mechanical stability, it comprehensively drives the degenerative cascade of the IVD and constitutes a pivotal pathological nexus intimately linked to clinical symptoms such as low back pain.

3.4. Aberrant invasion of nerves and vessels: characteristics of the degenerative microenvironment and the basis for pain

Degeneration of the CEP is not merely a localized breakdown of matrix homeostasis; it actively remodels the microenvironment of the IVD. This transition is characterized by the breakdown of the "metabolic and mechanical barrier" through two interrelated pathological processes: revascularization and innervation.[16,17]

3.4.1. Pathological revascularization: drivers, origins, and the "rheumatoid arthritis–like" cascade. Unlike the physiological devascularization occurring during skeletal maturation (see Section 2.2.1), the revascularization of the adult CEP is a pathological hallmark of disc degeneration. This process is driven by a synergistic interplay between biochemical recruitment and structural failure.[9,10]

Evidence suggests that revascularization is an actively recruited "angiogenic switch". Degenerating CEP cells, particularly those shifting toward an inflammatory fate 1 trajectory, robustly secrete proangiogenic factors such as VEGF and chemokines like chemokine (C-C motif) ligand 3 (CCL3) and chemokine (C-X-C motif) ligand 12 (CXCL12). These signals actively chemoattract vascular endothelial cells from the adjacent vertebral bone marrow. While matrix breakdown—such as the loss of antiangiogenic Chm-I—reduces the tissue's inherent resistance, the proinflammatory secretory phenotype serves as the primary engine for vessel infiltration.

Physically, recent ultrastructural evidence by Salman et al.[11] reveals that these pathological vessels originate from the bone marrow and penetrate the disc through micro-fissures at the CEP–BEP interface. The progressive separation of the CEP from its bony anchor creates micron-scale gaps that serve as essential conduits for vascular endothelial cell migration. Similar to the synovial pannus in rheumatoid arthritis, these invading vessels act as "Trojan horses", depositing catabolic elements, matrix-degrading enzymes (matrix metallopeptidases/a disintegrin and metallopeptidase with thrombospondin type I motifs [MMPs/ADAMTS]), and inflammatory cells into the previously sequestered disc compartments. This "rheumatoid arthritis–like" scenario facilitates a systemic inflammatory provocation that fundamentally accelerates disc decay.[18,19]

3.4.2. Aberrant innervation: the nociceptive basis of discogenic pain. Closely coupled with revascularization is the pathological ingrowth of sensory nerve fibers—a process termed aberrant innervation. In healthy adults, the CEP is largely aneural; however, in degenerated or painful discs, protein gene product 9.5 (PGP9.5)-positive nerve endings are frequently detected penetrating deep into the cartilaginous matrix and even the NP.

These invading nerves, often accompanying the newly formed "neurovascular bundles", primarily consist of nociceptors expressing neuropeptides such as substance p (SP) and calcitonin gene-related peptide (CGRP). The drivers for this neural invasion are multifaceted.

3.4.2.1. Neurotrophic signaling. Degenerating CEP cells and infiltrating MA release neurotrophic factors, including nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), which provide chemotactic cues for axonal sprouting.

3.4.2.2. Biomechanical and chemical sensitization. The loss of interfacial integrity and the resulting mechanical instability generate aberrant nociceptive signals. Furthermore, the acidic microenvironment (caused by lactate accumulation) and inflammatory cytokines (e.g., Interleukin-1 beta [IL-1β]) directly activate sensory endings via acid-sensing ion channel 1a (ASIC1a) channels and other receptors.

The co-invasion of nerves and vessels signifies the functional transformation of the CEP from an "inert" mechanical interface into an active source of nociception. This structural–biochemical link provides the anatomical basis for chronic discogenic low back pain, positioning the CEP as a critical therapeutic target for pain management.[20]

4. The core aspects of degeneration: porosity, permeability, and interfacial integrity

Functioning as the "lifeline" regulating the nutrition and metabolism of the IVD, the effectiveness of the CEP function is directly dependent on its transport properties. Understanding the porosity (the fraction of void space within the tissue available for fluid), hydraulic permeability (the ability to allow fluid passage under a pressure gradient), and the interfacial integrity between the CEP and the BEP is central to elucidating how degeneration physically disrupts internal homeostasis.

4.1. Fundamental principles of porosity, permeability, and nutrient exchange

The CEP's nutrient transport function relies on both passive diffusion and convection. Porosity determines the volume fraction of physical space available for solute diffusion. Hydraulic permeability reflects the ease with which interstitial fluid, carrying solutes, can flow through the CEP, driven by pressure differentials generated during daily disc loading–unloading cycles. Together, they constitute the CEP's "transport character": high porosity and permeability favor exchange, while low values create a barrier. The intrinsic factors governing these properties are the biochemical composition (such as collagen network density, proteoglycan content, and charge) and the structural state (such as degree of calcification) of the CEP matrix.

4.2. Impediment of permeability by calcification and the "nutrient deprivation hypothesis"

The "nutrient deprivation hypothesis" has long served as the cornerstone of endplate research. This traditional view posits that the progressive calcification and matrix densification of the CEP associated with aging or degeneration reduce its porosity and permeability, thereby impeding the diffusion of nutrients into the avascular central region of the disc. This ultimately leads to cellular metabolic failure and matrix degradation.

Multiple studies support this paradigm. The seminal work by Benneker et al.[21] in 2004 provided key anatomical evidence, finding a significant negative correlation between the density of capillary bud openings on the BEP and the severity of disc degeneration. Furthermore, Wong et al.[22] provided functional evidence by demonstrating that interindividual variability in CEP solute diffusion coefficients directly correlates with the survival and matrix synthesis levels of co-cultured NP cells. These findings established a clear pathophysiological sequence: degenerative matrix changes reduce permeability, leading to nutrient "starvation" and subsequent disc decay.

However, recent advancements have fostered a critical theoretical dialogue by introducing the "Interfacial Integrity Hypothesis". While the nutrient deprivation

model focuses on the biochemical permeability of the cartilage matrix itself, the interfacial integrity perspective shifts the focus to the mechanical and structural continuity of the CEP–BEP junction. Unlike the passive "starvation" envisioned in traditional theory, the interfacial hypothesis suggests that the physical separation of this interface—characterized by micro-fissures and the failure of adhesive bridges—may act as an active and potentially earlier initiator of degeneration. As suggested by Salman et al.,[11] this structural separation creates "permissiveness" for pathological revascularization and neuroinflammation, which can drive the degenerative cascade even before significant declines in nutrient diffusion are measurable.

In essence, while the nutrient deprivation hypothesis emphasizes the "barrier" function, the interfacial integrity hypothesis highlights the "anchoring" and "sealing" functions of the endplate. Both paradigms provide essential insights into different stages or phenotypes of IDD.

In summary, a consensus is emerging that CEP function is governed by the synergy between matrix permeability and structural anchoring. It is now understood that CEP matrix health and CEP–BEP interfacial integrity jointly determine the functional lifespan of the IVD. Both aspects must be preserved to effectively halt or reverse the degenerative process at the disc–vertebra interface.

4.3. A new perspective: the centrality of interfacial integrity and re-evaluating the role of the BEP

With the advancement of research techniques, particularly the precise quantification of the endplate system's ultrastructure and poromechanics, the linear model of the traditional "nutrient deprivation hypothesis" is being complemented and refined. Emerging evidence suggests that the matrix properties of the CEP itself and the integrity of its interface with the BEP may play more critical roles than changes in the bony structure of the BEP and that alterations in BEP porosity *per se* may not be the primary driver of degeneration.

Core evidence for this new perspective comes from a re-examination of the CEP–BEP interface. An ultrastructural study by Salman et al. in 2025[11] first revealed that the integration between the human lumbar CEP and BEP is not fully continuous; instead, micron-scale gaps bridged only by fragile, fine fibrous "adhesive bridges" commonly exist. The width of these interfacial gaps showed a significant positive correlation with age, degeneration severity, and disc calcification and was associated with an increased number of vascular channels within the adjacent BEP. This indicates that the mechanical integrity of the interface itself is a vulnerable link in maintaining normal endplate system function. Its separation not only directly compromises mechanical anchorage but also provides a physical entry point for aberrant vascular invasion, inflammation, and ectopic calcification, potentially constituting an initiating event for degeneration and pain.

Concurrently, quantitative studies on the poromechanics of the endplate system have prompted a re-evaluation of the BEP's role. In 2021, research by Malandrino et al.[23] based on micro-computed tomography data and computational modeling, revealed that although the porosity and hydraulic permeability of human BEP exhibit substantial inter-individual variability and potential age-related changes, these parameters showed no statistical association with the degeneration grade of the adjacent IVD. Computational simulations further demonstrated that even extreme values of BEP porosity and permeability are not key determinants regulating solute concentration or volume changes within the disc. Instead, the study indicated that the properties of the BEP exert their biological effects primarily by influencing the local fluid velocity within the adjacent CEP, suggesting a mechanobiological coupling mechanism rather than a mere physical diffusion barrier.

Consequently, the current integrated view posits that during IDD, pathological alterations in the CEP matrix (e.g., calcification, GAG loss) directly impair its diffusive permeability, while the progressive separation of the CEP–BEP interface compromises the structural integrity of the system and triggers aberrant biological responses (vascularization, neural ingrowth, inflammation). In contrast, changes in the porosity of the bony portion of the BEP may be more of an accompanying phenomenon or a secondary regulatory factor, rather than the primary cause of nutritional failure. This understanding shifts the therapeutic focus away from the simplistic concept of "BEP sclerosis" toward the more modifiable targets of "CEP matrix health" and "interfacial integrity maintenance", thereby opening new avenues for the development of treatment strategies.

5. Research models: species selection and model construction

5.1. Comparative anatomy of the CEP across species: fundamental differences between humans and other animals and the need for cautious extrapolation

Animal models are indispensable tools for investigating the physiological and pathological mechanisms of the CEP. However, the fundamental differences in the developmental stage, tissue architecture, and cellular phenotype of the CEP among species pose significant challenges for experimental design and the extrapolation of findings. A clear understanding of these differences is a prerequisite for ensuring the scientific validity and clinical relevance of research.[24]

Systematic comparative anatomical studies have revealed significant distinctions between the CEP of species ranging from rodents to large animals and that of humans. Histological analysis by Zhang et al.[25] in 2014 indicated that the key differences lie in the persistence of the growth plate and the degree of development of the BEP. In adult mice and rats, the CEP is directly contiguous with a persistently active skeletal growth plate, and the BEP layer is very thin or indistinct. In rabbits and sheep, the CEP possesses a defined BEP structure but remains adjacent to residual growth plate tissue. In stark contrast, the adult human CEP is fundamentally different: the growth plate is completely closed and absent.

The CEP exists as a permanent, often calcified, layer of hyaline cartilage that is densely integrated with a well-developed BEP. This means that the CEP of commonly used quadrupedal animals in their adult state remains in a developmentally "immature" condition compared with humans.[26]

Further molecular and biochemical characterization has deepened this understanding. In 2020, Lakstins et al.[27] found that the CEP of bovines and canines diverges from that of humans across multiple levels. Structurally, the cartilaginous layer of the CEP in bovines and canines is thinner, while the BEP is thicker. In terms of matrix composition, the sulfated GAG content in canine CEP is significantly higher than in humans. Cellularly, human CEP cells exhibit an elongated, spindle-shaped morphology arranged in parallel, whereas bovine and canine cells are more rounded and lack organized alignment. Regarding gene expression profiles, bovine CEP shows higher expression of matrix synthesis-related genes, whereas the spontaneously degenerating canine CEP generally presents a hypo-anabolic phenotype.[28]

These fundamental differences carry important implications for research: there is no single "ideal" animal model that fully replicates all characteristics of the human CEP. For instance, bovine CEP, being relatively closer to human CEP in matrix composition, may be more suitable for studying the fundamental biomechanics and physiological regulation of the CEP. Conversely, the spontaneous disc degeneration model in chondrodystrophic dogs (e.g., dachshunds) holds unique value for exploring pathological mechanisms and therapeutic interventions due to its ability to recapitulate disease progression and clinical correlations. While rodent models facilitate genetic manipulation, their distinctly different developmental context demands high caution in mechanistic studies, and their limitations must be carefully considered when extrapolating conclusions to humans. Therefore, species selection must be closely aligned with the specific scientific question at hand, with a clear awareness of the inherent anatomical differences of the model.[29]

In summary, the selection of an appropriate animal model requires a careful balance between anatomical fidelity and research feasibility. For instance, bovine CEP models, owing to their matrix composition and collagen/proteoglycan ratios being remarkably similar to humans, are exceptionally well-suited for investigations into fundamental CEP biomechanics and permeability. Conversely, the spontaneous degeneration model in chondrodystrophic dogs (e.g., dachshunds) uniquely recapitulates the progressive revascularization and pain-related clinical correlates of human disease. This makes canine models particularly valuable for exploring long-term pathological mechanisms and validating novel therapeutic interventions for discogenic pain. Researchers should therefore select a species that specifically aligns with their investigative focus—whether that be the physical properties of the "metabolic interface" or the complex biological landscape of the "degeneration initiator".

5.2. Commonly used small animal models for CEP degeneration: direct injury versus indirect instability?

After selecting an appropriate species, the methodology for inducing disc and CEP degeneration represents another crucial decision. Based on the mode of intervention and the initiating principle of degeneration, mainstream animal models can be categorized into two major classes: direct injury models and mechanical instability models. Each possesses distinct characteristics and value in simulating the disease process, particularly concerning their impact on the CEP.

5.2.1. Direct injury models: NP puncture, annulotomy, etc. Models such as needle puncture of the NP or surgical incision of the AF induce degeneration by directly compromising the structural integrity of the AF with surgical instruments, leading to NP herniation or exposure. This rapidly triggers acute injury and subsequent degeneration of the disc.[30–33]

The advantages of these models lie in their relative simplicity to perform, technical maturity, and their ability to induce clear, reproducible degenerative changes within a relatively short timeframe (weeks). These changes include NP dehydration, proteoglycan loss, and secondary alterations in the CEP (e.g., a propensity for calcification). Therefore, they are highly suitable for assessing the consequences of degeneration or for testing regenerative therapies aimed at repairing already damaged discs, such as cell transplantation or biomaterial implantation.

However, a critical limitation of these models is the unphysiological nature of the degeneration trigger. The changes observed in the CEP within this model paradigm represent a "secondary effect" consequent to the primary NP injury, the release of inflammatory factors, and a dramatic shift in the mechanical environment. This makes it difficult for researchers to distinguish whether CEP degeneration results from its own primary dysfunction or is merely a passive response to injury in adjacent tissues. Consequently, this limitation restricts the utility of direct injury models in investigating the CEP's potential role as an "initiating factor" or an "independent regulator" in the degenerative cascade.

5.2.2. Mechanical instability models (e.g., lumbar spine instability surgery model). This type of model induces segmental spinal instability by surgically disrupting the stabilizing structures of the posterior column (e.g., supraspinous/interspinous ligaments, facet joints) without directly manipulating the disc, thereby simulating chronic, abnormal dynamic loading.[34]

The primary advantage of this model lies in the indirect and clinically relevant initiation of pathology, which more closely mirrors the chronic degenerative processes in humans caused by mechanical overload, poor posture, or degenerative instability. Studies have shown that in the lumbar spine instability (LSI) model, signs of CEP degeneration (e.g., increased apoptosis, worsened histological scores) can precede significant morphological changes in

the NP and AF.[35] This phenomenon makes the LSI model an ideal tool for investigating how abnormal mechanical stress directly acts upon and drives the primary degeneration of the CEP.

Precisely because of this characteristic, the LSI model is increasingly employed to elucidate the mechanobiological mechanisms underlying CEP degeneration. For instance, research utilizing this model has clarified how aberrant mechanical stress, via pathways such as the Hippo-YAP signaling axis[36] and Piezo1 ion channels,[37] regulates CEP cell fate and matrix metabolism and triggers osteoclast-mediated endplate remodeling. Therefore, for mechanistic studies aimed at dissecting how the CEP senses and transduces abnormal mechanical signals, and acts as the "epicenter" of the degenerative cascade, mechanical instability models provide an indispensable *in vivo* research platform.

In summary, model selection should be driven by the core scientific question. Direct injury models offer high efficiency for studying late-stage degenerative phenotypes or therapeutic interventions. In contrast, mechanical instability models possess greater physiological relevance and exploratory value for elucidating the primary degenerative mechanisms and the initial role of the CEP under abnormal mechanical loads. Employing both models in combination may allow for a more complete revelation of the CEP's complex role in IDD across different temporal scales and pathological stages (Table 3).

6. Advances in molecular and cellular mechanisms of CEP degeneration

With the established recognition of the CEP's central role in IDD, the underlying molecular and cellular mechanisms of its degeneration have become a focal point of research. Recent investigations have not only uncovered intrinsic metabolic dysregulation within CEP cells but have also elucidated how these cells sense and respond to aberrant biomechanical signals, thereby driving a cascade of events from cellular phenotypic switching to tissue remodeling.

6.1. Dysregulation of ECM metabolism

Matrix homeostasis is the biochemical foundation of CEP function; its disruption serves as the primary effector of structural decay. The physiological function of the CEP is highly dependent on the integrity and appropriate biochemical composition of its ECM. The essence of degeneration is a severe disruption of the homeostatic balance between ECM synthesis and degradation, manifesting as inhibited anabolism and heightened catabolism. Ultimately, this metabolic imbalance renders the CEP vulnerable to external stressors, shifting the focus from intrinsic biochemical decay to extrinsic mechanical provocation.[38,39]

On the anabolic side, the suppressed expression of key transcription factors (e.g., SRY-box transcription factor 9 [SOX9]) directly leads to reduced synthesis of core matrix components such as type II collagen and aggrecan. Concurrently, enzymes responsible for ECM assembly and cross-linking may also become dysfunctional.

On the catabolic side, a suite of matrix-degrading enzymes is abnormally activated. These include: MMPs, such as MMP-13, which efficiently degrade type II collagen; and ADAMTS, such as ADAMTS-4/ADAMTS-5, primarily responsible for cleaving the core protein of proteoglycans. The activity of these enzymes is strongly induced by proinflammatory factors and further amplified by signaling pathways such as oxidative stress.

This metabolic imbalance leads to qualitative changes in the CEP's ECM: disorganization of the collagen network, decreased proteoglycan content and water-retention capacity, and aberrant mineral deposition. The direct consequences are the concurrent decline of the CEP's mechanical properties and its transport characteristics.

Table 3

Comparison and selection guide for experimental models of CEP degeneration.

Model category	Representative methods	Suitable research questions	Advantages	Limitations
Direct injury models	Needle puncture; annulotomy; large-bore suction	Evaluation of late-stage degenerative phenotypes; testing of intradiscal regenerative therapies	Technically straightforward; rapid and highly reproducible degenerative changes	Nonphysiological initiation; CEP changes are often secondary to NP/AF trauma
Mechanical instability models	LSI surgery; bipedal/upright posture models	Investigating CEP as the primary initiator; mechanobiology of stress-induced decay	Clinically relevant trigger; allows observation of CEP changes before significant NP loss	Longer induction period; higher surgical complexity and variability in instability levels
Ex vivo/explant models	Bovine/porcine CEP explants in bioreactors	Solute diffusion coefficients; nutrient permeability; baseline matrix biomechanics	Controlled environment; direct measurement of transport properties; human-like matrix density	Lacks systemic factors (immune response, nerve/vessel ingrowth) and dynamic spinal loading
Spontaneous models	Chondrodystrophic dogs (e.g., beagle, dachshund); sand rats	Natural disease progression; pathological revascularization; pain-related behavior studies	High fidelity: naturally recapitulates the "vascular-to-calcified" transition and clinical pain correlates	Significant maintenance costs; ethical considerations; long-term study duration

AF = annulus fibrosus; CEP = cartilaginous endplate; LSI = lumbar spine instability; NP = nucleus pulposus.

More critically, the ECM fragments generated during degradation can themselves act as damage-associated molecular patterns, which, by activating signaling pathways such as those involving toll-like receptors, further exacerbate the local inflammatory response. This creates yet another vicious cycle that propels degenerative progression. Therefore, restoring normal ECM metabolic balance in CEP cells represents a fundamental goal for intervention against its degeneration.

6.2. Mechanotransduction

The CEP is not only a metabolic barrier but also a primary mechanosensor; when matrix integrity is compromised, cells become increasingly sensitized to aberrant loading. The CEP continuously experiences and adapts to complex mechanical loads throughout life, with abnormal stress being a primary inducer of its degeneration. Research has revealed sophisticated pathways through which CEP cells convert mechanical stimuli into biochemical signals.[40]

Studies have shown that abnormal compressive forces activate the mechanosensitive ion channel piezo-type mechanosensitive ion channel component 1 (Piezo1) on the CEP cell membrane, triggering downstream nuclear factor kappa B (NF-κB) signaling, which in turn upregulates the expression of the RNA acetyltransferase n-acetyltransferase 10 (NAT10). NAT10 enhances the stability of mechanistic target of rapamycin (mTOR) mRNA by catalyzing its N4-acetylcytidine (ac4C) modification, leading to increased mTOR protein levels. The hyperactive mTOR pathway subsequently inhibits cytoprotective autophagy, ultimately exacerbating CEP cell apoptosis and disrupting matrix metabolism. This pathway elucidates how mechanical overload can compromise cellular self-repair capacity through epitranscriptomic regulation.[37]

Other research has found that under abnormal dynamic loading, such as in lumbar spinal instability, the mechanosensitive Hippo signaling pathway is activated in CEP cells. This activation leads to the inactivation and cytoplasmic retention of its downstream effector, yes-associated protein (YAP). The loss of YAP activity relieves its transcriptional repression of the chemokine *CCL3* gene, prompting CEP cells to secrete large amounts of CCL3. CCL3 recruits and promotes the aggregation and differentiation of osteoclast precursors at the endplate site, initiating the resorption and ossific remodeling of the CEP and forming the characteristic porous, "cheese-like" endplate. This mechanism seamlessly connects the entire process from mechanical sensing to intercellular communication and finally to tissue-level remodeling, explaining how abnormal mechanical forces drive the structural decay of the endplate.[41]

6.3. Oxidative stress and inflammation

The degenerative CEP microenvironment is typically characterized by excessive accumulation of reactive oxygen species (ROS) and chronic low-grade inflammation. These two processes mutually reinforce each other, forming a vicious cycle that accelerates tissue damage. A key link in this process is the dysregulation of the cellular antioxidant defense system.

The master antioxidant transcription factor, nuclear factor erythroid 2-related factor 2 (Nrf2), plays a protective role. Expression levels of Nrf2 are significantly downregulated in degenerated human CEP tissue and in rat models. Research has found that the compound 4-octyl itaconate (4-OI) can stabilize and activate Nrf2 by inhibiting its ubiquitination-mediated degradation, which is facilitated by the E3 ubiquitin ligase zinc finger protein 598 (ZNF598). Activated Nrf2 translocates to the nucleus, initiating the expression of a suite of downstream antioxidant enzymes and phase II detoxifying enzymes. This enhances the clearance of excess ROS, suppresses CEP cell apoptosis and excessive catabolism, and alleviates disc degeneration in whole animal models. This mechanism underscores the importance of maintaining Nrf2 pathway homeostasis for combating oxidative damage in the CEP.[42]

Furthermore, inflammation and oxidative stress are closely intertwined. Immune cells such as MA that infiltrate the degenerated CEP, along with the CEP cells themselves, can produce large quantities of proinflammatory factors (e.g., tumor necrosis factor-alpha [TNF-α], IL-1β). These factors not only directly induce the expression of matrix-degrading enzymes but also further promote ROS generation and inhibit matrix synthesis. On the other hand, abnormal mechanical stress or an acidic microenvironment (e.g., due to lactate accumulation) can directly activate CEP cells or adjacent nerve endings, leading to ASIC1a-mediated apoptosome formation and exacerbating the local inflammatory response.[43] Therefore, oxidative stress and inflammation constitute a destructive positive-feedback loop that persistently undermines the vitality and function of CEP cells. Beyond direct cellular damage, the resulting oxidative microenvironment can induce long-term alterations in the cellular program via epigenetic modifications.

6.4. Epigenetic regulation

Epigenetic modifications play a pivotal role in maintaining CEP cell homeostasis. Studies have found that in degenerated CEP, the expression of the histone methyltransferase enhancer of zeste 2 polycomb repressive complex 2 subunit (EZH2) is significantly upregulated. EZH2 catalyzes trimethylation of histone H3 at lysine 27 (H3K27me3), creating a repressive chromatin environment that specifically binds to and silences the promoter of the gene encoding SOX9, the master chondrogenic transcription factor. The downregulation of SOX9 directly leads to reduced synthesis of key matrix components, such as type II collagen and proteoglycans, compromising CEP integrity. This "EZH2-SOX9" axis reveals how epigenetic dysregulation programmatically shuts down the anabolic function of CEP cells at

the transcriptional level, promoting their degeneration. In animal models, inhibiting EZH2 or overexpressing SOX9 effectively alleviates CEP degeneration, confirming the critical role of this pathway.[43]

While this review focuses on the well-characterized EZH2-mediated histone modification axis, it is important to acknowledge that other epigenetic layers, such as microRNA regulation and DNA methylation patterns, also represent emerging and significant frontiers. Future research integrating these multilayered epigenetic networks will be essential for a more holistic understanding of CEP homeostasis.

6.5. Insights from single-cell landscapes: cellular heterogeneity and immune crosstalk

The transition from bulk tissue analysis to scRNA-seq has revolutionized our understanding of the cellular ecosystem within the CEP. While traditionally viewed as a relatively homogenous tissue, recent high-resolution transcriptomic profiling of human degenerative endplates has unveiled a complex landscape of cellular heterogeneity, identifying nine distinct cell clusters. These include seven chondrocyte subpopulations—CB, regulatory chondrocytes, homeostatic chondrocytes, prehypertrophic chondrocytes, fibrocartilage chondrocytes, proliferative chondrocytes, and hypertrophic chondrocytes (HTC)—alongside infiltrating MA and T/NK cells.[8]

6.5.1. Subpopulation-specific molecular signatures and transcriptional regulation. The identification of these clusters provides definitive molecular markers that resolve long-standing ambiguities regarding the CEP phenotype. The newly defined CB subpopulation, characterized by the expression of *CNMD* and *DCN*, appears to be the primary driver of chondrogenesis and mitosis, regulated by the transcription factor EGR1. In contrast, regulatory chondrocytes cells are enriched in genes such as *CFH* and *FRZB*, suggesting a specialized role in maintaining metal ion homeostasis and defending against oxidative stress. Crucially, the hypertrophic shift—a hallmark of CEP calcification—is mapped to the HTC cluster, which is uniquely governed by the transcription factor REL (a member of the NF-κB family). The activation of the REL-IRF1 axis in HTCs highlights an intrinsic link between terminal differentiation and the acquisition of a proinflammatory secretory phenotype, effectively bridging matrix mineralization with local inflammation.

6.5.2. Trajectory dynamics: the bifurcation of cell fates. Pseudotime trajectory analysis offers a dynamic temporal view of the degenerative process, suggesting that CEP cells undergo a directed phenotypic evolution rather than stochastic decay. During degeneration, chondrocytes appear to diverge into two distinct functional destinations: fate 1 (inflammatory-related): this trajectory is marked by the significant upregulation of complement activation markers and cytokine-related genes (e.g., *CFH*, *CHI3L1*, *CP*). Cells following this path actively contribute to the "inflammaging" of the endplate microenvironment. Fate 2 (homeostasis and ECM-related): this path is dominated by genes involved in matrix structural integrity and metabolic regulation (e.g., *JUN*, *FUS*, *COL1A1*). This bifurcation indicates that IDD may be driven by a systemic failure of cells to maintain the fate 2 homeostatic program, instead succumbing to the inflammatory cascades of fate 1.

6.5.3. The immuno-cartilage interface and intercellular communication. Perhaps the most transformative insight from scRNA-seq is the elucidation of the "immuno-cartilage" interface. The presence of MA and T/NK cells within the degenerative CEP microenvironment indicates that immune infiltration is a critical component of endplate pathology. Ligand–receptor interaction analysis using the cell–cell communication database (CellPhoneDB) has identified the FN1 (fibronectin)–$\alpha4\beta1/\alpha4\beta7$ complex as a primary mediator of the crosstalk between MA and chondrocyte subsets. Since FN1 is a major glycoprotein of the ECM, its interaction with chondrocyte integrins suggests that MA may actively remodel the CEP matrix and influence cell adhesion and fibrosis. Furthermore, T/NK cells appear to exert a regulatory influence on chondrocyte catabolism through cluster of differentiation 74 (CD74)-mediated signaling. This complex intercellular network suggests that the CEP is not merely a passive mechanical barrier but an active immunological hub. The recruitment of immune cells and their subsequent interaction with specific chondrocyte subsets likely accelerates the breakdown of the "nutrient lifeline", ultimately dictating the degenerative fate of the entire IVD.

7. Summary and outlook

7.1. Summary: the CEP—a hub for disc homeostasis and an epicenter of degeneration

This review systematically synthesizes multidimensional research on the CEP, spanning from its fundamental biology to the mechanisms of its degeneration. The accumulated evidence compellingly demonstrates that the CEP is far from a passive structural cover. Instead, it functions as a central hub in maintaining the internal homeostasis of the IVD. It integrates mechanical roles—such as anchoring and load buffering—with metabolic regulation, including nutrient diffusion and waste exchange. Its integrity directly dictates the fate of the disc. CEP degeneration is an active process initiated by alterations in matrix composition and cellular dysfunction, which subsequently leads to diminished physical transport properties and a loss of interfacial mechanical integrity. This process not only weakens the CEP's own functions but also, by triggering nutritional failure, aberrant mechanical stress transmission, neurovascular invasion, and local inflammation, drives and accelerates the cascading degeneration of the NP and AF. Ultimately, this process

becomes intimately linked with clinical symptoms such as discogenic pain. Therefore, regarding the CEP as a key target with independent pathophysiological significance is crucial for a comprehensive understanding and effective intervention in IVD degenerative disease.

7.2. Current research status and challenges

Despite the growing recognition of the CEP's importance, several significant challenges persist. First is the issue of definitional precision, as the CEP and BEP are frequently conflated in clinical imaging. Second, the anatomical disparities between humans and animal models limit the direct extrapolation of research findings. Third, and perhaps most critically, there is a distinct lack of noninvasive, CEP-specific biomarkers. Current imaging modalities struggle to quantify the early biochemical shifts in CEP permeability or cellular health, which is essential for early patient stratification and the monitoring of therapeutic efficacy.

7.3. Future therapeutic strategies: toward disease-modifying interventions

Moving forward, therapeutic strategies must shift from palliative symptom management to functional restoration of the CEP. Targeted interventions should focus on the following dimensions.

7.3.1. Improving permeability and matrix health. Strategies may include the development of inhibitors targeting ectopic calcification, such as ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1) inhibitors, or the application of anabolic growth factors like bone morphogenetic protein 7 (BMP-7) to promote type II collagen synthesis and restore the "metabolic lifeline".

7.3.2. Modulating mechanobiology. Precision targeting of key nodes in aberrant mechanotransduction pathways, such as Piezo1 ion channels or YAP signaling, could enable CEP cells to maintain homeostasis even under pathological mechanical loads.

7.3.3. Maintaining interfacial integrity. Utilizing bioactive scaffolds or adhesive biomaterials to reinforce the CEP–BEP interface, thereby preventing revascularization and neuroinflammation at the disc–vertebra junction.

7.3.4. Precision medicine via biomarkers. Identifying specific molecular signatures through multi-omics integration to enable personalized, endplate-driven therapies.

In summary, focusing the research lens on the CEP not only deepens the understanding of the fundamental nature of disc degeneration but also opens up entirely new therapeutic frontiers. Through interdisciplinary collaboration to overcome existing challenges, targeted protection and functional reconstruction of the CEP hold the potential to become a revolutionary strategy for halting or even reversing the degenerative disc process and alleviating associated pain at its source.

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Conflicts of interest

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Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Author contributions

JS—conception of the overall framework of this review and drafting of the original manuscript.
JM—data curation and critical revision of the manuscript.
FY and TL—literature investigation and formal analysis.
ZL—conceptualization, supervision of the entire research process, secured the necessary funding, and critical revision of the manuscript.
LY—supervision of the project, administered the resources and project management, secured funding, and critical revision of the manuscript.
PZ—conceptualization and supervision of the work, administered the project, secured funding, and critical revision of the manuscript.
DW—conceptualization, supervised the research, administered the project, and critical revision of the manuscript.

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