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Highlights

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ECM hybrid scaffolds decipher the dual code of organ aging

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Organ aging represents a systemic biological process, characterized by a coordinated decline in functionality across various organ systems. This process underpins cardiovascular pathologies and exacerbates age-related comorbidities, including neurodegenerative disorders, metabolic syndrome, and immunosenescence. Elucidating the cross-tissue regulatory mechanisms governing this decline is pivotal for advancing human healthspan and devising targeted interventions to mitigate age-related degeneration. Importantly, the field is transitioning from descriptive observations toward mechanism-driven therapeutic strategies. Regenerative approaches now aim to restore organ functional homeostasis not solely via cellular replacement but through reprogramming the aging tissue microenvironment.[1] A pivotal consensus review identified extracellular matrix (ECM) remodeling as the 13th hallmark of aging,[2] acknowledging ECM as a mechanistic contributor to degeneration mediated by dynamic bidirectional signaling, thereby overturning its historical perception as a static scaffold. Moreover, it underscores the ECM's dual role as both a structural framework and a dynamic signaling entity, whose spatiotemporal evolution determines tissue regenerative competence[3] (Fig. 1).

Beyond serving as a passive scaffold, the ECM functions as a dynamic regulatory hub. It integrates its biochemical composition—such as laminin conformations, elastin-derived matrikines, and glycosaminoglycan sulfation patterns—with mechanical cues (eg, rigidity, viscoelasticity) to orchestrate tissue morphostasis through multiscale interactions.[4] Key mechano-biochemical axes, including integrin–FAK–ERK and Piezo1–Ca^{2+} signaling, directly regulate cellular programs such as proliferation, differentiation, autophagy, and senescence.[5,6] In the aging myocardium, pronounced network dysregulation manifests in pathological stiffening (>15 kPa compared with <5 kPa in youth), primarily driven by lysyl oxidase (LOX)-mediated collagen crosslinking and elastin degradation.[7] Simultaneously, aberrant undersulfation of chondroitin sulfate glycosaminoglycans impairs heparan sulfate proteoglycan-dependent growth factor sequestration, while hyaluronan fragmentation generates proinflammatory damage-associated molecular patterns (DAMPs).[8] These biochemical alterations interact synergistically with micromechanical degradation, triggering a self-perpetuating injury cascade. Crucially, aged ECM persistently activates the integrin α11–DDR2 complex,[9] thereby inducing compensatory cardiomyocyte apoptosis, promoting myofibroblast differentiation, and accelerating excessive collagen deposition. This triad leads to interstitial and perivascular fibrosis, ventricular stiffening, and irreversible systolic and diastolic dysfunction.

Conventional models cannot replicate the biochemical-mechanical coupling in aged ECM, limiting mechanistic studies of cardiac aging.[7] Isolated biochemical analyses lack the physico-structural context required to capture critical phenomena such as fiber tension-regulated integrin clustering or strain-dependent collagen conformational switching. While tunable synthetic hydrogels (eg, polyacrylamide, polyethylene glycol) enable precise control of bulk tissue elasticity, they fail to reproduce native ECM ligand biochemistry—including conformation-specific integrin-binding motifs, MMP-cleavable domains, hypoxia-responsive cryptic peptides, and time-resolved DAMP release kinetics. Consequently, 2 fundamental knowledge gaps persist. First, the synergistic interplay between age-specific biochemical cues and mechanical stimuli remains unquantified, particularly regarding their role in driving degenerative signaling cascades. Second, bioengineering challenges exist in developing stimuli-responsive matrices that concurrently halt the fibrotic stiffening cycle and reactivate endogenous regenerative pathways.

To address these challenges, the DECIPHER (Decellularized ECM-Coupled Synthetic Hydrogel) scaffold developed by the National University of Singapore team represents a paradigm-shifting innovation in material science (Fig. 2A). This system integrates polyacrylamide hydrogels with decellularized cardiac tissue through a 3-step process. First, formaldehyde-functionalized acrylamide solution infiltrates tissue slices and forms covalent bonds with proteins during ultraviolet (UV) crosslinking, preventing structural collapse in subsequent decellularization. Second, an optimized sodium deoxycholate (SDC)/DNase treatment preserves over 95.8% of collagen and glycosaminoglycans while maintaining native fiber architecture. This preservation is confirmed by collagen alignment metrics revealing 23% higher branch-point density in aged ECM. Third, orthogonal stiffness tuning achieves physiologically relevant stiffness levels (approximately 10 kPa for youthful or 40 kPa for aged conditions) without

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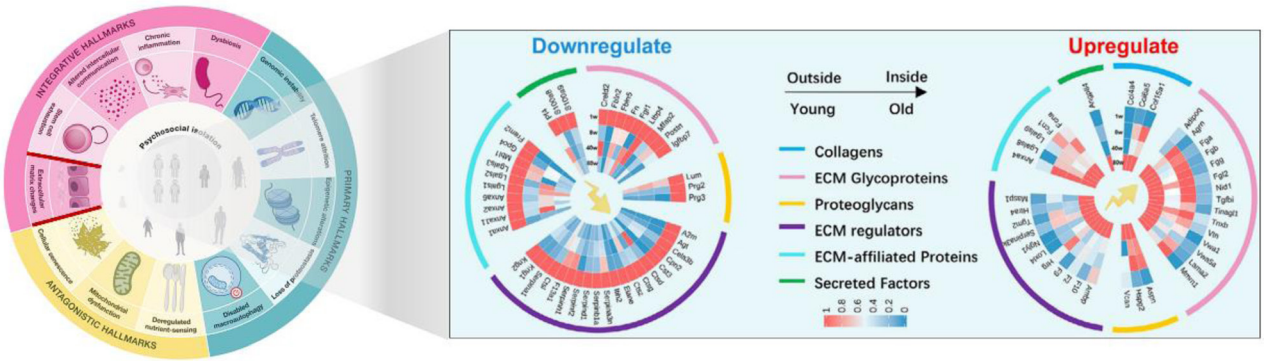

Figure 1. ECM as a central regulator of multiscale aging hallmarks. Adapted with permission from Kroemer et al.[2] and Liu et al.[3]

altering ligand presentation (Fig. 2B). The hybrid scaffold preserves over 95.8% of collagen and glycosaminoglycans, with scanning electron microscopy confirming collagen fiber morphology consistent with native tissue (Fig. 2C). Crucially, the interpenetrating hydrogel–ECM network replicates physiological viscoelasticity, overcoming limitations of conventional elastic scaffolds. This platform reveals that young ECM biochemical ligands override high-stiffness signaling. Aged cardiac fibroblasts (CFs) cultured on young ECM substrates exhibit significantly suppressed α-SMA expression and reduced stress fiber formation. This suppression persists even under high-stiffness conditions that simulate aged cardiac environments (Fig. 2D). Concurrently, yes-associated protein (YAP) nuclear translocation is blocked (Fig. 2E), maintaining CFs in a quiescent state. Conversely, aged ECM substrates activate CF senescence regardless of the mechanical environment.

CFs exhibit age-dependent responses to ECM signals. Young CFs demonstrate integrated mechanosensing, characterized by stiffness-induced α5 integrin clustering and ECM age-regulated β3 expression. In stark contrast, aged CFs display mechanosensing impairment. Zyxin—a mechanosensitive actin regulator—requires both aged ECM ligands and high stiffness for significant upregulation. Conversely, LOX-mediated collagen crosslinking increases 3.2-fold exclusively on aged ECM substrates, independent of mechanical stiffness (Fig. 2F). Notably, aged CFs cultured on young ECM exhibit a rejuvenation-like response, marked by downregulation of senescence markers such as p53. Native ECM architecture critically determines functional outcomes. Conventional reconstituted films with fragmented fibers elevate α-SMA expression by 2.3-fold. In contrast, DECIPHER-preserved fibrillar structures suppress pathological CF activation by maintaining ligand spatial orientation, evident in collagen fiber-guided CF migration patterns. Mechanistically, young ECM maintains homeostasis by elevating matrix metalloproteinase (MMP2/3) expression, whereas aged ECM drives collagen crosslinking via increased LOX activity, exacerbating myocardial stiffening (Fig. 2G). These findings challenge the prevailing view that mechanical signals dominate fibrotic progression.

The DECIPHER platform establishes a transformative foundation for targeted regenerative interventions by leveraging its unique capacity to decouple ECM properties. This dynamic decoupling enables precise engineering of therapeutic strategies. Young ECM-derived ligands (eg, laminin α5 peptides) can be formulated into nanotherapeutics to disrupt fibrotic cascades. Separately, targeting senescence receptors such as anti-integrin α11 antibodies or crosslinking enzymes (eg, LOXL2 inhibitor PXS-5505) might reverse pathological collagen crosslinking and activate endogenous repair mechanisms. Innovatively, the platform's ability to convert native ECM into functional bioink facilitates the construction of patient-specific aging models using autologous fibroblasts. These models enable high-throughput screening of combination therapies (eg, YAP inhibitors + LOXL2 blockers) tailored to individual ECM phenotypes, thereby optimizing anti-fibrotic efficacy. Critically, the mechanistic insights from DECIPHER reveal that ECM biochemical composition dominates over mechanical signaling in driving aging phenotypes. This redefines the ECM as the central orchestrator of senescence pathways, overturning reductionist mechanobiology-centric paradigms and establishing a universal framework for multiorgan rejuvenation. The conserved molecular signatures of ECM stiffening and ligand dysregulation observed across cardiac, hepatic, and renal pathologies enable synchronized multiorgan regeneration through targeting unified pathways such as the integrin β3-STAT3 axis or LOXL2-mediated collagen crosslinking.

Building on this paradigm shift, DECIPHER's spatiotemporal recombination of ECM properties provides a foundational platform to accelerate regenerative medicine's transition from passive tissue repair toward active biological age reversal. Future integration with single-cell spatial multiomics will elucidate context-dependent ECM remodeling dynamics across aging trajectories, while the incorporation of photo-responsive hydrogels aims to engineer adaptive microenvironments for precision rejuvenation.[10] Within such next-generation systems, light-triggered release of young ECM peptides is projected to dynamically suppress pathological crosslinking, and patient-derived induced pluripotent stem cell (iPSC)-based aging models are expected to enable high-throughput screening of mechanistically informed combination therapies. This synergistic convergence—spanning material science, multiomics, and synthetic biology—will ultimately decipher the competitive-synergistic dynamics governing ECM-driven aging, unlocking molecular blueprints for scalable organ regeneration.

Collectively, this breakthrough represents a transformative advancement in programmable aging research. By reprogramming the ECM into a modifiable biological framework that is decodable, rewritable, and functionally implementable, this approach deciphers molecular-level blueprints for organ regeneration. This paradigm shift enables precision medicine to evolve from reactive therapeutic correction toward proactive rejuvenation strategies, ultimately advancing healthy aging.

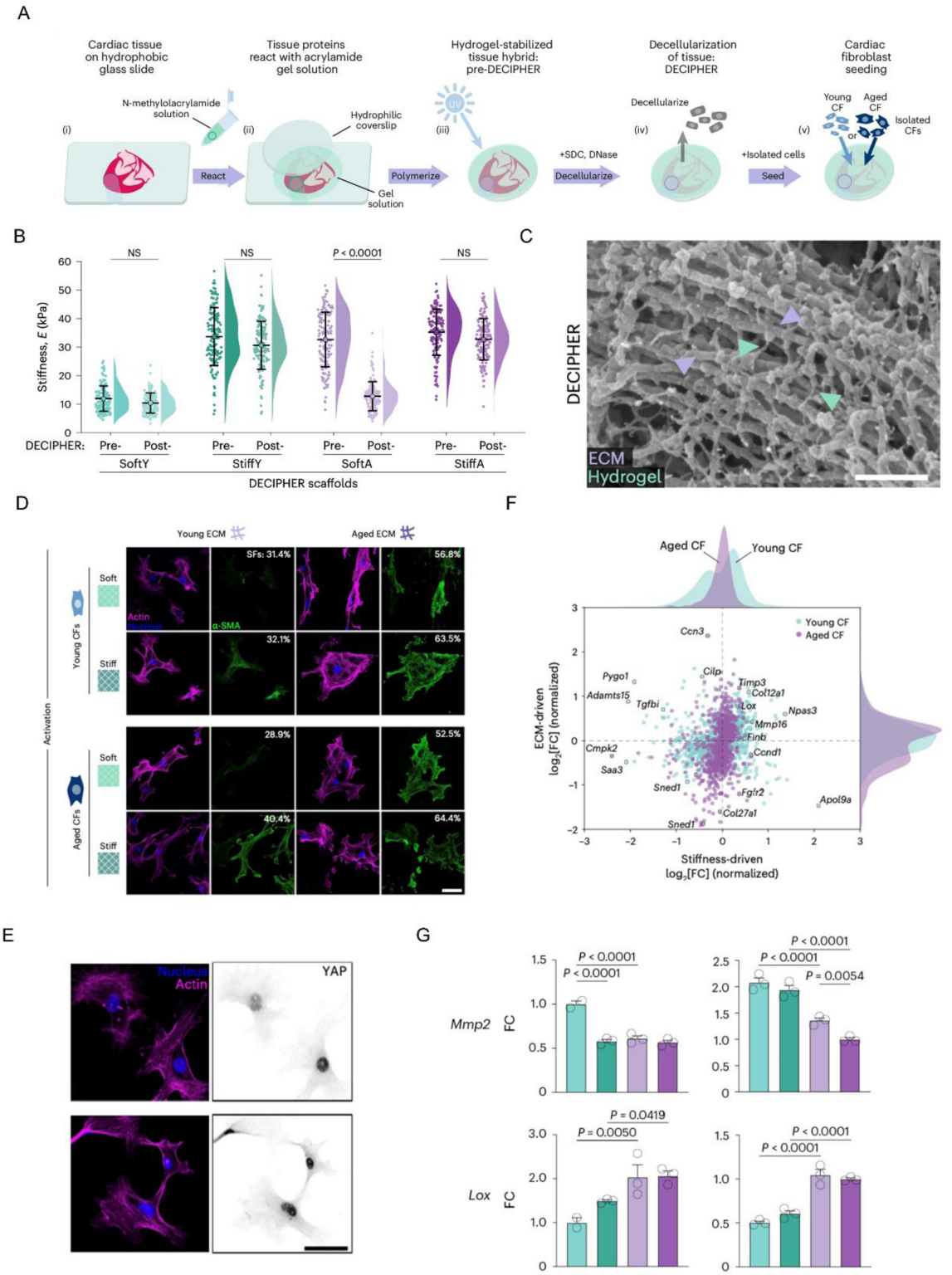

Figure 2. DECIPHER platform illustrates the biochemical and mechanical hallmarks of cardiac aging. (A) Schematic representation of DECIPHER hydrogel fabrication. (B) Stiffness mapping of DECIPHER samples highlights the tunable mechanical properties of the scaffold. Samples exhibited baseline stiffness (SoftY, StiffA), increased stiffness (StiffY), or decreased stiffness (SoftA) following treatment. (C) Scanning electron microscopy (SEM) images showing the microstructural features of DECIPHER samples. (D) Immunofluorescence images of young CFs cultured on SoftY and StiffY DECIPHER substrates, showing nuclear staining (blue), α-SMA (purple), and cytoskeletal structures (green). (E) Immunofluorescence images of young CFs cultured on SoftY and StiffY DECIPHER substrates, showing nuclear staining (blue), YAP localization (purple), and cytoskeletal structures (green). (F) Scatter plot depicting normalized log2(FC) values of 957 differentially expressed genes (DEGs) in DECIPHER samples, driven by substrate stiffness (x-axis) or ECM composition (y-axis). Data are shown for young (purple) and aged (cyan) CFs, with marginal probability densities illustrating the distribution of stiffness- and ECM-driven genes for each age group. (G) Normalized gene expression (mean ± SEM) of Lox, Mmp2, and Col12a1 across experimental conditions. Adapted with permission from Sun al.[7]

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Conflicts of interests

The authors declare that they have no conflicts of interest.

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