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EDITORIAL

Extracellular matrix guides the fate of organoids

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Cells without an extracellular matrix (ECM) are like performers without a stage—formless masses with no environment to enact their roles. The secreted ECM is critical for organoid form and function, as cells exist in and continuously modify the ECM, a complex assembly of proteins, glycosaminoglycans, and water that governs processes across the spectrum of function from morphogenesis to repair.[1] Alterations in this tightly regulated system have profound consequences, exemplified by fibrosis, where excessive ECM deposition disrupts physiologic function.[2] The ECM dictates bulk properties of tissues, such as the stiffness imparted by fibrous proteins, directional strength arising from anisotropic collagen alignment, and elasticity from elastin.[3] Despite its central role, the study of ECM has been constrained by limited experimental platforms: *in vivo* analyses suffer from technical barriers to imaging, while conventional polystyrene culture systems fail to capture physiological function. Therefore, experimental platforms must be designed to allow simultaneous investigation of cells and their secreted ECM to fully understand this dynamic reciprocity[4] between cells and their secreted ECM.

A myriad of biomaterial systems have been developed to reproduce specific aspects of ECM architecture and function.[5] Traditional monophase hydrogels, for instance, may be engineered with tunable mechanical and biochemical cues, whereas fibrous scaffolds fabricated by electrospinning or self-assembly better replicate native architecture. These simplified platforms often present cells—typically a single cell type—with only a uniform background, neglecting both the influence of neighboring cell populations and the vast repository of ECM that cells naturally secrete. Emerging evidence[6,7] describes the critical importance of secreted ECM to the cellular interpretation of biomaterial platforms. As a result, traditional hydrogel systems do not fully recapitulate the reciprocal feedback loops that define tissue-level behavior. Organoid-based systems that are permissive to secreted ECM dynamics are essential, as they allow cells to establish and modify their own microenvironment with spatiotemporal precision while engaging in meaningful cross-talk with surrounding cells, ideally multiple cell types, to better mimic tissue-level organization. Such platforms provide a more physiologically relevant framework for studying the interplay of cell–ECM interactions (Table 1).

Organoid systems engineered with biomaterials permissive to secreted ECM—and the resultant dynamic reciprocity—have shown promise in studying organoid maturation, organoid disease modeling, and organoid morphogenesis. For example, Chrisnandy and Lutolf[8] demonstrated an eight-arm polyethylene glycol-based culture system that supported the secretion of laminin-332 in intestinal organoid culture, leading to the expression of regeneration and maturation markers and organoid formation. Others have shown that hydrogel systems supportive of laminin and collagen IV secretion supported alveolar organoid function.[9] Radically simple

Table 1. Comparison of traditional engineered systems and the secreted ECM-enabled system

Feature	Traditional engineered systems	Secreted ECM–permissive organoid systems
Matrix source	Synthetic (e.g., alginate) or purified protein (e.g., collagen)	Endogenously secreted by cells
Cell-matrix interaction	Unidirectional (cells respond to preset cues)	Bidirectional (cells modify and respond to their ECM)
Heterogeneity	Uniform environment	Spatially heterogeneous, multi-cell-type environments
Maturation potential	Limited	Enhanced morphogenesis and functional maturation
Disease modeling	Limited to preset cues	Captures emergent patient-specific ECM remodeling

Abbreviation: ECM: Extracellular matrix.

approaches, such as organoid culture in alginate without any additional chemical or biological cues, have succeeded too, likely due to the secreted ECM.[10] Furthermore, disease modeling is enhanced in organoid systems permissive to ECM secretion. Morais *et al.*[11] discovered altered ECM organization in a patient-derived induced pluripotent stem cells kidney organoid that could potentially contribute to patient-specific therapeutic development. Ultimately, the secreted ECM drives morphogenesis by integrating structural support, mechanical cues, and biochemical signals to direct cell behavior and tissue organization. A mammary gland organoid system permissive to collagen secretion demonstrated fundamental insights into ductal branch elongation and epithelial self-organization.[12]

Volume 1, Issue 3 of *Organoid Research* features seven contributions that collectively showcase the breadth and translational potential of organoid research. The article "Global Research Trends in Bone/Cartilage Organoid from 2010 to 2024: A Bibliometric and Visualized Study" provides a systematic analysis of the developmental trajectory and global hotspots in the field.[13] "Bridging Molecular Mechanisms and Therapeutic Innovations: The Role of Brain Organoids in Neurodevelopmental Disorder Research" explores how brain organoid models connect fundamental biology with therapeutic discovery in neurodevelopmental disorders.[14] In "Organoids as a Platform for Personalized Antisense Oligonucleotide Screening: Advancing Precision Medicine," the potential of organoids in facilitating patient-specific antisense oligonucleotide drug development is highlighted.[15] The review "Tendon Organoids Advances in Bioengineering Strategies and Translational Applications" discusses innovative approaches for tendon repair and regeneration.[16] Similarly, "Bone Marrow Microenvironment and Organ Chips: Advances in Tumor Dormancy Research" provides insights into how organotypic systems can reveal the dynamics of cancer cell dormancy.[17] The review "Construction Strategy of Rotator Cuff Organoids" presents a novel framework for engineering rotator cuff—specific organoids, emphasizing scaffold selection, cellular composition, and biomechanical conditioning to better model musculoskeletal physiology and pathology.[18] Finally, the perspective "Advancing Musculoskeletal Organoids Research: Overcoming Barriers to Reduce Animal Model Dependency" addresses challenges and future directions for reducing reliance on animal experimentation.[19] Across these diverse topics, several contributions underscore the indispensable role of the ECM, both as a scaffold for organoid development and as a dynamic regulator of cell fate and tissue function. Together, these articles exemplify the diversity of organoid applications, spanning bibliometric mapping, neurological and musculoskeletal research, oncology, virology, and precision medicine.

In conclusion, the ECM is far more than a passive scaffold—it is an active and dynamic regulator of cell behavior, tissue mechanics, and morphogenesis. Traditional biomaterials for organoid culture have enabled important insights but remain limited in their ability to capture the reciprocal feedback between cells and their secreted ECM. Organoid-based systems that allow cells to deposit, remodel, and respond to their own ECM offer a transformative step forward, providing physiologically relevant platforms that support functional maturation, enable patient-specific disease modeling, and uncover fundamental mechanisms of tissue organization. Future work should develop strategies to stabilize or selectively enrich certain ECM proteins, to control their incorporation and assembly within the extracellular milieu, and to capture gradients of matrix-bound growth factors that emerge during tissue development. The continued integration of biomaterial design with the organoid field holds immense promise for advancing both basic discovery and translational applications.

Conflict of interest

Nicholas G. Fischer is an Editorial Board Member of this journal and declared that he has no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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