Zur Y, et al., J Stem Cell Res Dev Ther 2021, 7: 086
DOI: 10.24966/SRDT-2060/100086

HSOA Journal of
Stem Cells Research, Development & Therapy

Short Commentary

Extracellular Matrix Scaffolds - A Tissue-Specific Bioactive Niche for Stem Cells in Regenerative Therapy

Yehonatan Zur, Tzila Davidov, Limor Baruch and Marcelle Machluf*

Faculty of Biotechnology & Food Engineering, Technion - Israel Institute of Technology, Haifa, 3200003, Israel

Keywords: ECM hydrogel; Extracellular matrix; Regenerative therapy; Tissue-specific

Aiming to restore the normal function of diseased or injured tissues, regenerative therapy approaches are generally based on the engineering of complex tissue-mimicking grafts, encompassing biomaterial scaffolds, stem cells, or their combinations [1-4]. Due to the major role of stem cells in physiological regenerative mechanisms, regenerative therapies normally rely on either stem cells transplantation or stem cell recruitment from the neighboring tissue into the implanted scaffold. The design of grafts that provide a supportive bioactive microenvironment for stem cells is, thus, crucial for its ability to control and direct stem cells' fate towards the induction of reparative processes [5,6]. Such microenvironment can be provided through the careful selection of biomaterials and their engineering processes, thus considering their structural properties as well as their ability to support cell-biomaterial interactions through diverse biochemical and biophysical cues.

The Extracellular Matrix (ECM) is the physiological structural support of all tissues, and it plays an important role in controlling the tissue's cellular processes such as cell proliferation, migration, and differentiation [7]. The use of decellularized ECM from different sources in its native structure or processed through different technologies is, therefore, considered an excellent candidate biomaterial for regenerative therapy scaffolds [8,9]. The ECM's source or tissue of origin, however, was not always deemed a relevant concern [10].

***Corresponding author:** Marcelle Machluf, Faculty of Biotechnology & Food Engineering, Technion - Israel Institute of Technology, Haifa, 3200003, Israel, E-mail: machlufm@bfe.technion.ac.il

Citation: Zur Y, Davidov T, Baruch L, Machluf M (2021) Extracellular Matrix Scaffolds - A Tissue-Specific Bioactive Niche for Stem Cells in Regenerative Therapy. J Stem Cell Res Dev Ther 7: 086.

Received: December 05, 2021; **Accepted:** December 13, 2021; **Published:** December 20, 2021

In our recent work [11], we studied porcine ECM (pECM)-based hydrogels derived from cardiac, artery, pancreas, and adipose tissues, thus exploring their common and distinct attributes and their relevance for regenerative therapy. This study demonstrated that while pECM hydrogels derived from different tissues share major componential and structural similarities, their minor differences make each hydrogel a unique scaffold that is most suitable to different applications depending on the biological, mechanical, and physical demands. For example, the adipose tissue-derived hydrogel is mechanically weaker than the cardiac one, which is expected due to their different physiological roles. Cardiac pECM hydrogel will, therefore, be a better choice for applications where mechanical support is required. Furthermore, through diverse cell-ECM interactions, each pECM hydrogel grants its residing stem cells a particular tissue-specific microenvironment that dictates their proliferation rate and morphology. Most importantly, pECM hydrogels derived from the different tissues had directed the spontaneous differentiation of human induced pluripotent stem cells (hiPSCs) towards the lineages typical of each pECM original tissue. This tissue-specific spontaneous differentiation was demonstrated through the expression of markers that are specific for cells residing in each tissue of origin, but also through a comprehensive gene expression sequencing analysis that revealed unique gene expression profiles for cells on each pECM hydrogel.

Tissue-specific effects of ECM-based scaffolds were previously observed in scaffolds processed through different fabrication techniques such as soft lithography, electrospinning, and 3D printing [12]. Offering a rich variety of scaffold options like sheets [13], microcarriers [14,15], hydrogels [16], and 3D constructs [17], they can address numerous medical needs, thus emphasizing the advantages of using ECM-based materials derived from the target organ [18]. In a paper by Gao et al. [19], for instance, a bio-ink was developed from decellularized ECM and alginate. They succeeded in preserving the ECM attributes and constructing blood vessels using 3D coaxial printing technology. Using a mouse model, the researchers demonstrated that the ECM-based blood vessel graft promoted stem cells survival, engraftment efficiency, endothelial differentiation, and tissue repair; alas the graft had weak mechanical strength. Another example is the electrospinning of ECM, which can produce scaffolds that closely mimic the fibrous structures of native ECM, support cell functions and nutrient transport. In our earlier work [20], we have developed an electrospun scaffold composed solely of decellularized porcine cardiac ECM and demonstrated the ability of this scaffold to support the bioactivity and viability of cultured human mesenchymal stem cells (hMSCs), hiPSCs, and Neonatal rat cardiomyocytes (rCM). Furthermore, processed ECM can be functionalized with different biomolecules, such as growth factors and drugs to achieve a more specific effect on cells and tissues. This was demonstrated by Sonnenberg et al. [21], who had incorporated hepatocyte growth factor (HGF-f) within pericardial pECM hydrogel as a treatment for myocardial infarction (MI). The delivered HGF-f was shown to prevent cell death and promote angiogenesis. Moreover, *In-vivo* rat model experiments demonstrated that the HGF-f loaded ECM hydrogel had preserved or improved cardiac function, increasing vascularization, and reducing fibrosis, compared to ECM hydrogel alone or HGF-f in saline.

Unveiling the preservation of ECM's tissue-specific attributes through its processing to hydrogel and other fabrication techniques paves the path to the design of ECM-based scaffolds that are reproducible and well-defined. Such scaffolds can circumvent batch-to-batch variability, which is the major disadvantage of ECM as a natural biomaterial; while still benefit its structural advantages and tissue-specific bioactivity to support stem cells. Nevertheless, for these scaffolds to gain translational impact, further standardization approaches should be applied to ensure repeatable outcomes, particularly in terms of cell-ECM interactions. One promising approach is harnessing new technologies such as next-generation proteomics to quantify the retention of native ECM components. This relatively new technology enables in depth examination of the matrisome [22-24], which together with artificial intelligence tools such as DeepMind's AlphaFold [25] can predict protein structures. Consequently, these technologies can facilitate both componential and structural standardization.

In summary, ECM-based scaffolds produced through diverse processing technologies hold tremendous potential as a tissue-specific supportive niche for stem cells in diverse regenerative therapies. Furthermore, the ability to direct stem cells fate through the choice of ECM source, together with prospective standardized manufacturing processes can significantly expedite the clinical translation of such ECM-based platforms.

References

1. Ntege EH, Sunami H, Shimizu Y (2020) Advances in regenerative therapy: A review of the literature and future directions. Regenerative Therapy 14: 136-153.
2. Chen FM, Zhang J, Zhang M, An Y, Chen F, et al. (2010) A review on endogenous regenerative technology in periodontal regenerative medicine. Biomaterials 31: 7892-7927.
3. Gomes ME, Rodrigues MT, Domingues RMA, Reis RL (2017) Tissue engineering and regenerative medicine: new trends and directions - A year in review. Tissue Eng Part B Rev 23: 211-224.
4. Howard D, Buttery LD, Shakesheff KM, Roberts SJ (2008) Tissue engineering: Strategies, stem cells and scaffolds. J Anat 213: 66-72.
5. Wang A, Tang Z, Park IH, Zhu Y, Patel S, et al. (2011) Induced pluripotent stem cells for neural tissue engineering. Biomaterials 32: 5023-5032.
6. Tuan RS, Boland G, Tuli R (2003) Adult mesenchymal stem cells and cell-based tissue engineering. Arthritis Res Ther 5: 32-45.
7. Frantz C, Stewart KM, Weaver VM (2010) The extracellular matrix at a glance. J Cell Sci 123: 4195-4200.
8. Badylak SF (2005) Regenerative medicine and developmental biology: The role of the extracellular matrix. Anat Rec B New Anat 287: 36-41.
9. Krishtul S, Baruch L, Machluf M (2020) Processed Tissue–Derived Extracellular Matrices: Tailored Platforms Empowering Diverse Therapeutic Applications. Advanced Functional Materials 30: 1-26.
10. Piez KA (1997) History of extracellular matrix: A personal view. Matrix Biol 16: 85-92.
11. Davidov T, Efraim Y, Hayam R, Oieni J, Baruch L, et al. (2021) "Extracellular Matrix Hydrogels Originated from Different Organs Mediate Tissue-Specific Properties and Function. Int J Mol Sci 22: 11624.
12. Zhang X, Chen X, Hong H, Hu R, Liu J, et al. (2021) Decellularized extracellular matrix scaffolds: Recent trends and emerging strategies in tissue engineering. Bioactive Materials 10: 15-31.
13. Feng Y, Jiang Z, Zhang Y, Miao X, Yu Q, et al. (2020) Stem-cell-derived ECM sheet-implant complexes for enhancing osseointegration. Biomaterials Science 8: 6647-6656.
14. Yu C, Kornmuller A, Brown C, Hoare T, Flynn LE (2017) Decellularized adipose tissue microcarriers as a dynamic culture platform for human adipose-derived stem/stromal cell expansion. Biomaterials 120: 66-80.
15. Sivandzade F, Mashayekhan S (2018) Design and fabrication of injectable microcarriers composed of acellular cartilage matrix and chitosan. J Biomater Sci Polym Ed 29: 683-700.
16. Saldin LT, Cramer MC, Velankar SS, White LJ, Badylak SF (2017) Extracellular matrix hydrogels from decellularized tissues: Structure and function. Acta Biomaterialia 49: 1-15.
17. Do AV, Khorsand B, Geary SM, Salem AK (2015) 3D Printing of Scaffolds for Tissue Regeneration Applications. Adv Healthc Mater 4: 1742-1762.
18. Efraim Y, Schoen B, Zahran S, Davidov T, Vasilyev G, et al. (2019) 3D Structure and Processing Methods Direct the Biological Attributes of ECM-Based Cardiac Scaffolds. Scientific Reports 9: 1-13.
19. Gao G, Lee JH, Jang J, Lee DH, Kong JS, et al. (2017) Tissue Engineered Bio-Blood-Vessels Constructed Using a Tissue-Specific Bioink and 3D Coaxial Cell Printing Technique: A Novel Therapy for Ischemic Disease. Advanced Functional Materials 27: 1-12.
20. Schoen B, Avrahami R, Baruch L, Efraim Y, Goldfracht I, et al. (2017) Electrospun Extracellular Matrix: Paving the Way to Tailor-Made Natural Scaffolds for Cardiac Tissue Regeneration. Advanced Functional Materials 27: 1-9.
21. Sonnenberg SB, Rane AA, Liu CJ, Rao N, Agmon G, et al. (2015) Delivery of an engineered HGF fragment in an extracellular matrix-derived hydrogel prevents negative LV remodeling post-myocardial infarction. Biomaterials 45: 56-63.
22. Hynes RO, Naba A (2012) Overview of the matrisome-An inventory of extracellular matrix constituents and functions. Cold Spring Harbor Perspectives in Biology 4: 2012.
23. Li Z, Tremmel DM, Ma F, Yu Q, Ma M, et al. (2021) Proteome-wide and matrisome-specific alterations during human pancreas development and maturation. Nat Commun 12: 1020.
24. Naba A, Clauser KR, Ding H, Whittaker CA, Carr SA, et al. (2016) The extracellular matrix: Tools and insights for the 'omics' era. Matrix Biol 49: 10-24.
25. Jumper J, Evans R, Pritzel A, Green T, Figurnov M, et al. (2021) Highly accurate protein structure prediction with AlphaFold. Nature 596: 583-589.

HERALD

Advances In Industrial Biotechnology | ISSN: 2639-5665

Advances In Microbiology Research | ISSN: 2689-694X

Archives Of Surgery And Surgical Education | ISSN: 2689-3126

Archives Of Urology

Archives Of Zoological Studies | ISSN: 2640-7779

Current Trends Medical And Biological Engineering

International Journal Of Case Reports And Therapeutic Studies | ISSN: 2689-310X

Journal Of Addiction & Addictive Disorders | ISSN: 2578-7276

Journal Of Agronomy & Agricultural Science | ISSN: 2689-8292

Journal Of AIDS Clinical Research & STDs | ISSN: 2572-7370

Journal Of Alcoholism Drug Abuse & Substance Dependence | ISSN: 2572-9594

Journal Of Allergy Disorders & Therapy | ISSN: 2470-749X

Journal Of Alternative Complementary & Integrative Medicine | ISSN: 2470-7562

Journal Of Alzheimers & Neurodegenerative Diseases | ISSN: 2572-9608

Journal Of Anesthesia & Clinical Care | ISSN: 2378-8879

Journal Of Angiology & Vascular Surgery | ISSN: 2572-7397

Journal Of Animal Research & Veterinary Science | ISSN: 2639-3751

Journal Of Aquaculture & Fisheries | ISSN: 2576-5523

Journal Of Atmospheric & Earth Sciences | ISSN: 2689-8780

Journal Of Biotech Research & Biochemistry

Journal Of Brain & Neuroscience Research

Journal Of Cancer Biology & Treatment | ISSN: 2470-7546

Journal Of Cardiology Study & Research | ISSN: 2640-768X

Journal Of Cell Biology & Cell Metabolism | ISSN: 2381-1943

Journal Of Clinical Dermatology & Therapy | ISSN: 2378-8771

Journal Of Clinical Immunology & Immunotherapy | ISSN: 2378-8844

Journal Of Clinical Studies & Medical Case Reports | ISSN: 2378-8801

Journal Of Community Medicine & Public Health Care | ISSN: 2381-1978

Journal Of Cytology & Tissue Biology | ISSN: 2378-9107

Journal Of Dairy Research & Technology | ISSN: 2688-9315

Journal Of Dentistry Oral Health & Cosmesis | ISSN: 2473-6783

Journal Of Diabetes & Metabolic Disorders | ISSN: 2381-201X

Journal Of Emergency Medicine Trauma & Surgical Care | ISSN: 2378-8798

Journal Of Environmental Science Current Research | ISSN: 2643-5020

Journal Of Food Science & Nutrition | ISSN: 2470-1076

Journal Of Forensic Legal & Investigative Sciences | ISSN: 2473-733X

Journal Of Gastroenterology & Hepatology Research | ISSN: 2574-2566

Journal Of Genetics & Genomic Sciences | ISSN: 2574-2485

Journal Of Gerontology & Geriatric Medicine | ISSN: 2381-8662

Journal Of Hematology Blood Transfusion & Disorders | ISSN: 2572-2999

Journal Of Hospice & Palliative Medical Care

Journal Of Human Endocrinology | ISSN: 2572-9640

Journal Of Infectious & Non Infectious Diseases | ISSN: 2381-8654

Journal Of Internal Medicine & Primary Healthcare | ISSN: 2574-2493

Journal Of Light & Laser Current Trends

Journal Of Medicine Study & Research | ISSN: 2639-5657

Journal Of Modern Chemical Sciences

Journal Of Nanotechnology Nanomedicine & Nanobiotechnology | ISSN: 2381-2044

Journal Of Neonatology & Clinical Pediatrics | ISSN: 2378-878X

Journal Of Nephrology & Renal Therapy | ISSN: 2473-7313

Journal Of Non Invasive Vascular Investigation | ISSN: 2572-7400

Journal Of Nuclear Medicine Radiology & Radiation Therapy | ISSN: 2572-7419

Journal Of Obesity & Weight Loss | ISSN: 2473-7372

Journal Of Ophthalmology & Clinical Research | ISSN: 2378-8887

Journal Of Orthopedic Research & Physiotherapy | ISSN: 2381-2052

Journal Of Otolaryngology Head & Neck Surgery | ISSN: 2573-010X

Journal Of Pathology Clinical & Medical Research

Journal Of Pharmacology Pharmaceutics & Pharmacovigilance | ISSN: 2639-5649

Journal Of Physical Medicine Rehabilitation & Disabilities | ISSN: 2381-8670

Journal Of Plant Science Current Research | ISSN: 2639-3743

Journal Of Practical & Professional Nursing | ISSN: 2639-5681

Journal Of Protein Research & Bioinformatics

Journal Of Psychiatry Depression & Anxiety | ISSN: 2573-0150

Journal Of Pulmonary Medicine & Respiratory Research | ISSN: 2573-0177

Journal Of Reproductive Medicine Gynaecology & Obstetrics | ISSN: 2574-2574

Journal Of Stem Cells Research Development & Therapy | ISSN: 2381-2060

Journal Of Surgery Current Trends & Innovations | ISSN: 2578-7284

Journal Of Toxicology Current Research | ISSN: 2639-3735

Journal Of Translational Science And Research

Journal Of Vaccines Research & Vaccination | ISSN: 2573-0193

Journal Of Virology & Antivirals

Sports Medicine And Injury Care Journal | ISSN: 2689-8829

Trends In Anatomy & Physiology | ISSN: 2640-7752