Cellular Therapy and Transplantation (CTT). Vol. 12, No. 1, 2023
doi: 10.18620/ctt-1866-8836-2023-12-1-7-12
Submitted: 01 December 2022, accepted: 03 March 2023

Biomaterials in three-dimensional cell culture: bone and cartilage regeneration

Mehmet Filizfidan [1,2], Volkan Tekin [3], Asuman Özen [4]

[1] Stem Cell Institute, Interdisciplinary Department of Stem Cells and Regenerative Medicine, Ankara University, Ankara, Türkiye
[2] Faculty of Medicine, Department of Medical Biology, Selcuk University, Konya, Türkiye
[3] Department of Physiology, University of Health Sciences, Gulhane School of Medicine, Ankara, Türkiye
[4] Veterinary Faculty, Department of Histology and Embryology, Ankara University, Ankara, Türkiye

E-mail: mffmolmed@gmail.com

Citation: Filizfidan M, Tekin V, Özen A. Biomaterials in three-dimensional cell culture: bone and cartilage regeneration. Cell Ther Transplant 2023; 12(1): 7-12.

Summary

Cell cultures, which are used to study and explain the activities of the microenvironment of living organisms at the cellular level, have been developed using various models and have made significant contributions over time. Due to the insufficient polarity, division, and extracellular matrix (ECM) development of cells in two-dimensional (2D) culture media resulting into limited vital activities such as the representation of cell morphology, niche environment, differentiation, proliferation, drug metabolism, viability, matrix production, gene and protein expression, transition to the three-dimensional (3D) culture model has been increased. In this review, we discuss the importance of 3D culture systems and present an outline of the properties of biomaterials used to construct 3D scaffolds and their interactions with cells.

Keywords

Biomaterial, bone and cartilage, regeneration, cell culture, extracellular matrix, stem cell.

Introduction

Cell cultures have been used for more than a century to study the mechanisms underlying cellular behaviors such as growth, differentiation, migration, and proliferation under the influence of biochemical and biomechanical microenvironments in living organisms. These models have been developed under the laboratory environment to study biological mechanisms and processes by optimizing them to specific standards. These so-called *in vitro* models are also crucial for understanding the formation and functioning of tissues and organs, as well as ongoing *in vivo* processes [1]. Cell cultures are common *in vitro* tools used to enhance our understanding of cell biology, tissue morphology, disease mechanisms, drug action, protein production, and tissue engineering. Much of the research on cancer biology is based on *in vitro* experiments with two-dimensional cell cultures. In two-dimensional culture media, cells are unsuitable for artificial tissue production as they cannot fully express their characteristics. The main reason for this is that in 2D cultures, the cell membrane only partially interacts with the ECM such that its other part interacts with the culture medium. In fact, 2D cultures have many limitations, such as the disruption of interactions between the cellular and extracellular environments, changes in cell morphology and polarity, and type of division. These drawbacks have led to the development of three-dimensional culture techniques to create models that can better mimic *in vivo* conditions [2]. Although 2D cell cultures are still commonly used in research, recent studies are trending towards 3D culture applications due to their similarity to biochemical and biomechanical microenvironments [3, 4]. The use of 3D cell cultures has reportedly yielded more effective results in terms of morphology, the niche environment, differentiation, proliferation, drug metabolism, viability, matrix production, gene and protein expression, similarities to the *in vivo* environment, responses to stimuli, and general cellular activities [4, 5, 6]. Cells cultured in a 3D environment show a morphology similar to that of *in vivo* cells as they have similar polarization (7). Due to the limitations of 2D cell culture systems, there is an increased transition to 3D culture systems. 3D culture systems are promising in view of their significant contribution

to many advances achieved in the development of new drug therapies, cancer treatment, personalized treatment modeling using stem cells, and tissue engineering. It is foreseen that 3D cell culture systems will significantly contribute to human health through technological developments and biomaterial optimization.

Basic Components of 3D Cell Culture Media

Biocompatible and biodegradable biomaterials, living cells, and bioactive molecules constitute the main factors in a three-dimensional cell culture environment [8]. To date, two basic approaches, "top-down" and "bottom-up", have been used for biofabrication in the cell culture environment. The "top-down" approach uses conventional tissue engineering techniques, such that cells are seeded on tissue scaffolds with biocompatible and biodegradable properties, and are expected to proliferate in the scaffold and synthesize their own extracellular matrices. This approach can be used to produce thin avascular tissues such as skin tissue, bladder, and cartilage. However, due to limited vascularization and diffusion within biomimetic scaffolds, complex tissues with high cell density and metabolic demand, such as those of the kidney and liver, cannot be produced using this approach. As for the "bottom-up" approach, microscale tissue blocks are fabricated in specific microstructures and then combined to form larger complex tissue structures. When applying this approach, fabrication techniques such as microgel fabrication, self-assembling cell aggregates (cell spheroids), and cell sheet engineering can be used to fabricate tissue blocks [9, 10].

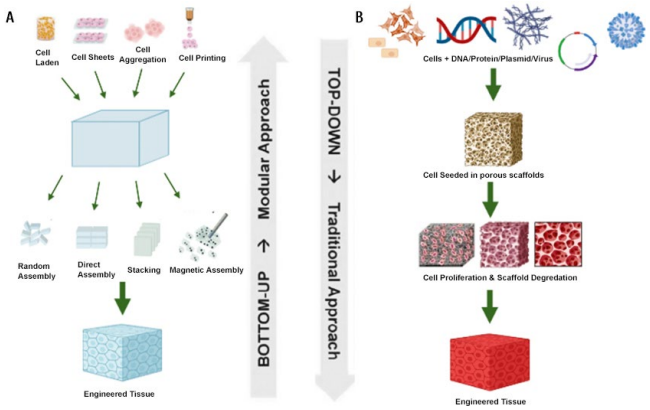


Figure 1. Shematic illustration of the Bottom-up and Top-down approach for tissue engineering

Establishing Integrity and Homeostasis in 3D Tissues

In conventional 2D cell cultures, adhesion occurs after cells are seeded into a glass or polystyrene Petri dish. This provides cells with basic mechanical support. In 2D cell culture models, cells have homogeneous access to molecules, such as nutrients and growth factors, in the medium [11]. Thus, under uniform conditions, cells show similar growth and reproductive activity [12]. However, because the two-dimensional cell culture environment does not reflect the *in vivo* microenvironment, various vital cellular events do not occur in this setting. It has been reported that the *in vivo* structural properties disappear due to the loss of polarization of the cells as well as very limited formation of the extracellular matrix. Polarization and extracellular matrix formation in cells are primary factors in the generation of 3D tissue structure [13].

In three-dimensional biomaterials, integrity and homeostasis are established by polarization, cell-cell interactions, and cell-matrix interactions. Extracellular matrices and molecular growth factors are combined to ensure cell proliferation. Furthermore, the niche environment is created that regulates tissue and organ development. Thus, cell survival and differentiation are optimized [14, 15, 16, 17]. The cells in live body have a three-dimensional microenvironmental structure. Cells maintain their vital activities depending on the interactions in this complex structure. These include polarization, cell-cell interactions, and cell-matrix interactions. The polarization resulting from these interactions maintains integrity and homeostasis of 3D tissues. Cell-cell and cell-matrix interactions are also critical for the continuity of the 3D structure and responses given to external stimuli [18].

In 3D cell cultures, cells show a polarization similar to that of *in vivo* conditions. Several changes have been reported to be observed by transplanting stem cells into the extracellular matrix, such as improvements in the apical-basal polarization, lumen formation, and proliferation, as well as numerous alterations at the gene and protein levels [19]. The good design of the 3D cell culture microenvironment is crucial to cell proliferation, migration, matrix synthesis, and terminal differentiation. Today, various 3D cell culture models are mostly used for gene and protein expression, genotoxic and cytotoxic research, and various R&D studies [12].

Interaction Between the Biomaterial Surface and Proteins

In 3D cell cultures, biomaterials first interact with water. Proteins of low molecular weight and high surface affinity contained in the biological fluid and synthesized by stem cells adhere to the surface of the biomaterial (The Vroman effect). They are later replaced by proteins with a larger molecular weight. It has been reported that this process, which involves transition from a nanometric to a micrometric size, can take from a few minutes to several hours [20, 21]. After the ECM proteins (laminin, fibronectin, collagen) reach the material surface, stem cells attach to the surface *via* integrin proteins. This phase, which occurs at a micrometric scale, can last up to several hours [22, 23, 24]. Once they have gained function, cells integrate with tissue. This phase of transition from the micrometric to the macrometric dimension can last from a few minutes to several hours [25]. The subunits of integrins (α, ß, γ) differ according to the type of ECM proteins. The major integrins involved in the interactions of stem cells with ECM proteins are alpha5beta1 for fibronectin, alpha2beta1 for collagen, and alpha6beta1gama1 for laminin. These interactions can be detected with the aid of a SEM (scanning electron microscope) and AFM (atomic force microscope). As a result of these interactions, intracellular signaling complexes are activated in stem cells [26]. Such interactions between ECM receptors and ligands initiate signal transduction cascades, resulting in a variety of cellular events that are important for repair and regeneration, including changes in cellular adhesion and migration and altered rates of proliferation and apoptosis. The presence

or extent of such changes may affect the balance of repair and regeneration responses, favoring one outcome over the other. Therefore, interventions that alter ECM signaling events may alter this balance to promote tissue regeneration and reduce scarring [27].

In tissue engineering applications, the choice of biomaterials for fabricating tissue scaffolds is of paramount importance. These materials serve as a model template for tissue regeneration and allow cells to adhere, transport, proliferate, and differentiate. The interaction between the biomaterial surface and proteins varies with the pH of the medium, temperature, ionic forces, and the presence of denatured substances. Electrostatic attraction, hydrogen bonds, hydrophobic interactions, and the pore structure of the surface play a role in the adsorption of proteins on the surface. In this context, the topography and chemical composition of the biomaterials are also crucial [23, 24]. Many of the biomaterials selected for the construction of tissue scaffolds lacking the surface properties required for cell-material interaction necessitates surface modifications. Surface modification is a method in which the properties of the surface are altered so that the selected material can serve as a suitable tissue scaffold. When modifying the surface, the bulk properties of the material remain the same, while the properties of the surface that comes into contact with the cells are changed. It has been reported that surface modification also allows for the binding of enzymes, drugs, antibodies, or other biologically active species to the surface by creating different functional chemical groups on the surface of the biomaterial. Surface modification techniques can be classified as physical, chemical, biological, and radiation methods [28]. When assessing the adhesion and proliferation of human fibroblast cells for different functional groups, it was determined that surfaces with amine (-NH2) and carboxylic acid (-COOH) groups yielded the highest rates of cell adhesion and proliferation. Lower cell adhesion and reduced spreading were observed on surfaces with methyl (-CH3), polyethylene glycol (-PEG), and hydroxyl (-OH) groups [29]. Microgroove surfaces, where extracellular matrix production and alkaline phosphatase activity are more intense than flat surfaces, have been shown to have considerable control over cellular behavior [30].

Biomaterials

Biomaterials are synthetic or natural nonliving materials used to restore or support the functions of tissues and organs in the living body [31]. The 1982 statement published by the National Institutes of Health Consensus Development Conference states, "Biomaterials are materials intended to be implanted in the body to correct and restore a missing or damaged function of the body and are defined as a composition of one or more non-pharmaceutical substances, whether natural or synthetic, in solid or sometimes liquid form, used in medical devices or biological systems" [32]. Biomaterials are widely used in fields such as medicine, pharmacy, bioengineering, and biotechnology. Biomaterials gain functionality by performing the same function in the relevant region of tissues and organs, which have degenerated as a result of trauma or injury. It is important that these materials meet the biological, physical, and mechanical properties of the tissue and organ for which they are used and adapt to the particular microenvironment. Therefore, it is important that the interactions at the cellular level are well understood and the biomaterials are carefully selected [33, 34].

Types of Tissue Scaffolds/Biomaterials for Tissue Engineering

Tissue scaffolds can be produced both naturally and synthetically using various methods and materials. In order for the relevant polymer to be used safely in tissue engineering studies, it should meet certain criteria. It is important that the biomaterial is bioinert. The interactions of bioinert materials with tissue are in the form of mechanical bonds. These bonds enable bioinert materials to adhere to cells without altering them [35]. Ideally, the biomaterial of tissue scaffolds should be biocompatible and biodegradable so that no immunological response is triggered after transplantation and the material is degraded in the body within the targeted time. It should be of a highly porous structure to allow for cell interaction and nutrient transfer. After the cells are seeded on the biomaterial, they must attach to specific functional groups to which they will bind. Thus, the biomaterial must have the appropriate surface chemistry to support the adhesion, survival, proliferation, and migration of the cells. The three-dimensional structure must be re-processable and mechanically durable. The degradation of biopolymers to monomers and the mechanical durability of the biopolymer until the cells produce their own extracellular matrix are both crucial. If these criteria are not fulfilled, severe complications may occur in the living being to which the grown tissue is transplanted. Synthetic polymers such as PGA, PLA, PLGA and natural polymers such as alginate, chitosan and collagen are widely used in the engineering of tissues such as cartilage, bone, skin, and connective tissue [36].

Scaffolds Used in Cartilage Treatment

To date, porous fibrous and hydrogel scaffolds have been used in studies for the treatment of cartilage. Oryan et al. evaluated the capacity of polylactic acid/polycaprolactone/hydroxyapatite (PLA/PCL/HA) composite scaffolds seeded with mesenchymal stem cells (MSCs) for regenerative bone treatment. It was observed that porous scaffolds were suitable and useful for the proliferation, osteogenesis and angiogenesis capabilities of mesenchymal stem cells. It has been reported that PLA/PCL/HA composite scaffolds seeded with mesenchymal stem cells increase the level of bone healing, and thus, are a potential candidate for treatment comparable to autograft repair [37]. In a systematic study of multi-substitute organic/inorganic scaffolding by Ressler et al. using freeze-gel casting, CaP (calcium phosphate) and chitosan-based highly porous composite scaffolds, substituted with Sr^{2+}, Mg^{2+}, Zn^{2+}, and SeO_3^{2-} ions, were constructed. It was observed that the components in the scaffold were very well bound to each other and displayed a highly porous structure with homogeneously distributed CaP particles. The scaffold showed high stability during the degradation process (28 days). The study results showed that ionic substitutions had a beneficial effect on cells and tissues. Scaffolds with multi-substituted CaP increased the expression of osteogenesis-related markers and phosphate residues, when compared to scaffolds with unsubstituted CaP [38]. Mesenchymal stem cells isolated from canine adipose tissue

have been differentiated to bone tissue by being seeded on a three-dimensional bio-scaffold constructed with biomaterials containing β-TCP and β-TCP/collagen [39]. In a study by Chandramohan et al. a biocomposite scaffold was constructed by mixing chitosan (CS), a natural polymer, and polycaprolactone (PCL), a synthetic polymer, to test its suitability for bone tissue engineering applications. Mesenchymal stem cells were seeded and grown in the resulting conditioned scaffold. The scaffold was coated with divalent zinc ions to impart osteogenic properties. The physico-chemical characterization of the scaffold was performed with XRD, SEM, and FTIR studies, and described as yielding positive results. Biological characterization showed that the scaffolds were compatible with MSCs and promoted osteoblast differentiation at both cellular and molecular levels. Increased calcium deposition in the cells was determined by alizarin red staining and ALP activity at cellular level. At molecular level, both the expression of osteoblast markers such as type 1 collagen and Runx2 mRNAs, and the level of the secretory proteins osteocalcin (OC) and osteonectin (ON) were determined to increase in the presence of tissue scaffolds. This study suggested that MSCs could be grown under standard *in vitro* conditions as well as in an *in vivo*-like environment, when seeded on a CS/PCL/Zn scaffold. It has been reported that CS/PCL/Zn scaffolds can serve as a potential biomaterial for bone tissue engineering applications [40]. In a study by Cao et al. it was aimed to support cartilage regeneration using the co-culture of bone marrow mesenchymal stem cells and costal chondrocytes (CChon). In this study, the researchers produced a biphasic scaffold consisting of a cell-encapsulated biodegradable gelatin methacrylate (GelMA) hydrogel in the upper layer and a macroporous poly(ε-caprolactone) (PCL) scaffold filled with cell-encapsulated GelMA hydrogel in the lower layer. PCL/GelMA biphasic scaffolds integrated with co-culture models have been reported to show excellent cartilage regenerative ability when implanted into the rat osteochondral defect model. *In vitro* and *in vivo* results have demonstrated that PCL/GelMA biphasic scaffolds integrated with the co-culture of BMSCs (bone marrow mesenchymal cells) and chondrocytes are promising for cartilage regeneration, and offer a novel approach to solving the fundamental problems of clinical cartilage repair [41]. Liu et al. designed a hybrid hydrogel scaffold mimicking the microenvironment of the osteochondral niches to overcome the challenge of integrated repair of osteochondral tissue. The results achieved with this three-dimensional (3D) cell culture also proved that the survival rate of the cells in the hybrid hydrogels doped with nHAP and dispersion was the highest. RT-qPCR analysis showed that genes related to osteoblasts and chondrocytes were expressed by bone mesenchymal stem cells after being cultured in nHAP-doped hydrogel scaffolds. It is considered that PHGD @nHAP hydrogel based on modified γ-PGA and HA mimicking the ECM of osteo-chondrocytes is a good candidate for tissue engineering scaffolds intended for integrated osteochondral repair [42].

Conclusions and Future Perspectives

Both 2D and 3D cell culture techniques are necessary for advancing research. Due to the limitations of 2D cell culture systems, there is an increased transition to 3D culture systems. The current understanding of ECM and its role in numerous cell functions and behaviors has given researchers an increasing interest in 3D cell culture. 3D cell culture has shown that it has the potential to completely change the way in which new drug treatments are tested, model diseases, stem cells and organ transplantation. As 3D cell culture becomes more widespread, techniques will be better understood and more advanced methods will emerge. Researchers currently working on it to test new therapies *via* 2D cell culture models should seriously consider 3D cell culture options. The benefits of co-culturing cells in 3D are superior to those of 2D cell cultures. As tissue engineering evolves, disease diagnosis and regenerative treatments will improve.

Financial support

This research received no grant from any funding agency/sector.

Ethical statement

This study does not present any ethical concerns.

Conflict of interest

The authors declared that there is no conflict of interest.

References

1. Rashidi H, Yang J, Shakesheff KM. Surface engineering of synthetic polymer materials for tissue engineering and regenerative medicine applications. Biomaterials Sci. 2014; 2:1318-1331. doi: 10.1039/C3BM60330J

2. Kapałczyńska M, Kolenda T, Przybyła W, Zajączkowska M, Teresiak A, Filas V, et al. 2D and 3D cell cultures – a comparison of different types of cancer cell cultures. Arch Med Sci. 2018; 14(4): 910-919. doi: 10.5114/aoms.2016.63743

3. Ravi M, Paramesh V, Kaviya S, Anuradha E, Paul Solomon F. 3D cell culture systems: Advantages and applications. J Cell Physiol. 2015; 230(1): 16-26. doi: 10.1002/jcp.24683

4. Duval K, Grover H, Han LH, Mou Y, Pegoraro AF, Fredberg J, Chen Z. Modeling physiological events in 2D vs. 3D cell culture. Physiology (Bethesda). 2017;32(4):266-277. doi: 10.1152/physiol.00036.2016

5. Morabito C, Steimberg N, Mazzoleni G, Guarnieri S, Fanò-Illic G, Mariggiò M. RCCS bioreactor-based modelled microgravity induces significant changes on *in vitro* 3D neuroglial cell cultures. Biomed Res Int. 2015, 754283. doi: 10.1155/2015/754283

6. Vunjak-Novakovic G, Martin I, Obradovic B, Treppo S, Grodzinsky A, Langer R, Freed L (1999): Bioreactor cultivation conditions modulate the composition and mechanical properties of tissue-engineered cartilage. J Orthop Res. 1999; 17(1), 130-138. doi: 10.1002/jor.1100170119

7. Vinci M, Gowan S, Boxall F, Patterson L, Zimmermann M, Court W, Lomas et al. Advances in establishment and analysis of three-dimensional tumor spheroid-based functional assays for target validation and drug evaluation. BMC Biol. 2012;10:29. doi: 10.1186/1741-7007-10-29

8. Karakecili A, Tigli ARS, Huri P. Tissue Engineering. In: Fundamentals of Biomedical Engineering, Asyal MH, Kara S, Yilmaz B (Eds.). 2014; Chapter 13: 433-475. Nobel Publishing House.

9. Lu T, Li Y, Chen T. Techniques for fabrication and construction of three-dimensional scaffolds for tissue engineering. Int J Nanomedicine. 2013;8:337-350. doi: 10.2147/IJN.S38635

10. Berthiaume F, Maguire TJ, Yarmush ML. Tissue engineering and regenerative medicine: history, progress, and challenges. Annu Rev Chem Biomol Eng. 2011;2:403-30. doi: 10.1146/annurev-chembioeng-061010-114257

11. Freshney, R.I. (2005) Culture of animal cells: A manual of basic technique. 5th Edition, Wiley, New York. doi: 10.1002/9780471747598

12. Edmondson R, Broglie JJ, Adcock AF, Yang L. Three-dimensional cell culture systems and their applications in drug discovery and cell-based biosensors. Assay Drug Dev Technol. 2014 May;12(4):207-218. doi: 10.1089/adt.2014.573

13. Choi SW, Yeh YC, Zhang Y, Sung HW, Xia Y. Uniform beads with controllable pore sizes for biomedical applications. Small. 2010; 6(14), 1492-1498. doi: 10.1002/smll.201000544

14. Dai X, Ma C, Lan Q, Xu T. 3D bioprinted glioma stem cells for brain tumor model and applications of drug susceptibility. Biofabrication. 2016; 8(4):045005. doi: 10.1088/1758-5090/8/4/045005

15. Mravic M, Péault B, James AW (2014): Current trends in bone tissue engineering. BioMed Res Int. 2014, 865270. doi: 10.1155/2014/865270

16. Banavar S, Trogdon M, Drawert B, Yi T, Petzold L, Campàs O. Coordinating cell polarization and morphogenesis through mechanical feedback. PLoS Comput Biol, 2021; 1, 1007971. doi: 10.1371/journal.pcbi.1007971

17. Wolf D, Ley K. Waking up the stem cell niche: How hematopoietic stem cells generate ınflammatory monocytes after stroke. Circ Res. 2015; 116(3): 389-392. doi: 10.1161/CIRCRESAHA.114.305678

18. Burdick JA, Vunjak-Novakovic G. Engineered microenvironments for controlled stem cell differentiation. Tissue Eng Part A. 2009; 15(2):205-219. doi: 10.1089/ten.tea.2008.0131

19. Huh D, Hamilton GA, Ingber DE. From 3D cell culture to organs-on-chips. Trends Cell Biol. 2011; 21(12):745-754. doi: 10.1016/j.tcb.2011.09.005

20. Vroman L. Effects of hydrophobic surfaces upon blood coagulation. Thromb Diath Haemorrh. 1964 ;10(2), 455-493. PMID: 14113384

21. Bacáková L, Filová E, Rypácek F, Svorcík V, Starý V. Cell adhesion on artificial materials for tissue engineering. Physiol Res. 2004; 53 Suppl 1:35-45. PMID: 15119934

22. Singhvi R, Kumar A, Lopez GP, Stephanopoulos GN, Wang DI, Whitesides GM, Ingber DE. Engineering cell shape and function. Science. 1994; 264(5159):696-698. doi: 10.1126/science.8171320

23. Steiner G, Tunc S, Maitz M, Salzer R. Conformational changes during protein adsorption. FT-IR spectroscopic imaging of adsorbed fibrinogen layers. Anal Chem. 2007. 79(4): 1311-1316. doi: 10.1021/ac061341j

24. Keselowsky BG, Collard DM, García AJ. Surface chemistry modulates fibronectin conformation and directs integrin binding and specificity to control cell adhesion. J Biomed Mater Res A. 2003; 66(2):247-259. doi: 10.1002/jbm.a.10537

25. Roach P, Eglin D, Rohde K, Perry CC. Modern biomaterials: a review – bulk properties and implications of surface modifications. J Mater Sci Mater Med. 2007;18(7):1263-1277. doi: 10.1007/s10856-006-0064-3

26. Mao Y, Schwarzbauer JE. Fibronectin fibrillogenesis, a cell-mediated matrix assembly process. Matrix Biol. 2005;24(6):389-399. doi: 10.1016/j.matbio.2005.06.008

27. Petreaca M, Martins-Green M. Cell-Extracellular Matrix Interactions in Repair and Regeneration. In *Principles of Regenerative Medicine (3rd Edition).* 2019; Academic Press, pp.15-35. doi: 10.1016/C2015-0-02433-9

28. Guney A, Kara F, Ozgen O, Aksoy EA, Hasirci V, Hasirci N. Surface modification of polymeric biomaterials. In: Biomaterials Surface Science. 2013. John Wiley & Sons., pp.89-158. doi: 10.1002/9783527649600.ch5

29. Faucheux N, Schweiss R, Lützow K, Werner C, Groth T. Self-assembled monolayers with different terminating groups as model substrates for cell adhesion studies. Biomaterials. 2004; 25(14):2721-2730. doi: 10.1016/j.biomaterials.2003.09.069

30. Ma Z, Mao Z, Gao C. Surface modification and property analysis of biomedical polymers used for tissue engineering. Colloids Surf B Biointerfaces. 2007; 60(2):137-157. doi: 10.1016/j.colsurfb.2007.06.019

31. Langer R, Vacanti JP. Tissue engineering. Science. 1993; 260(5110):920-926. doi: 10.1126/science.8493529

32. A consensus development conference: Clinical Applications of Biomaterials. JAMA. 1983; 249(8): 1050-1054. doi: 10.1001/jama.1983.03330320048031

33. Jiang J, Papoutsakis ET. Stem-cell niche based comparative analysis of chemical and nano-mechanical material properties impacting *ex vivo* expansion and differentiation of hematopoietic and mesenchymal stem cells. Adv Healthc Mater. 2013;2(1):25-42. doi: 10.1002/adhm.201200169

34. Fisher OZ, Khademhosseini A, Langer R, Peppas NA. Bioinspired materials for controlling stem cell fate. Acc Chem Res. 2010;43(3):419-428. doi: 10.1021/ar900226q

35. Dubok VA. Bioceramics – Yesterday, today, tomorrow. Powder metallurgy and metal ceramics. 2000; 39, 381-394. doi: 10.1023/A:1026617607548

36. Büyüköz M, Alsoy Aktınkaya S. The effects of porogen agent size and ınterconnection time on the mechanical properties of gelatin scaffold. CBU J Sci.2015; 11(2), 167-173. (Turk.). doi: 10.18466/cbujos.63838

37. Oryan A, Hassanajili S, Sahvieh S, Azarpira N. Effectiveness of mesenchymal stem cell-seeded onto the 3D polylactic acid/polycaprolactone/hydroxyapatite scaffold on the radius bone defect in rat. Life Sci. 2020; 257:118038. doi: 10.1016/j.lfs.2020.118038

38. Ressler A, Antunović M, Teruel-Biosca L, Ferrer GG, Babić S, Urlić I, et al. Osteogenic differentiation of human mesenchymal stem cells on substituted calcium phosphate/chitosan composite scaffold. Carbohydr Polym. 2022; 277:118883. doi: 10.1016/j.carbpol.2021.118883

39. Ozgenc O. Osteogenic Differentiation of Canine Adipose Derived Mesenchymal Stem Cells On *B-Tcp* and *B-* Tcp/Collagen Biomaterials. PhD Thesis. 2019. Ankara University Graduate Sch of H Sci, Ankara.

40. Chandramohan Y, Jeganathan K, Sivanesan S, Koka P, Amritha TMS, Vimalraj S, Dhanasekaran A. Assessment of human ovarian follicular fluid derived mesenchymal stem cells in chitosan/PCL/Zn scaffold for bone tissue regeneration. Life Sci. 2021; 264:118502. doi: 10.1016/j.lfs.2020.118502

41. Cao Y, Cheng P, Sang S, Xiang C, An Y. Wei X. Yan Y, Li P (2021): 3D printed PCL/GelMA biphasic scaffold boosts cartilage regeneration using co-culture of mesenchymal stem cells and chondrocytes: *In vivo* study. Mater Design. 2021; 210, 110065. doi: 10.1016/j.matdes.2021.110065

42. Liu S, Li P, Liu X, Wang P, Xue W, Ren Y, et al. Bioinspired mineral-polymeric hybrid hyaluronic acid/poly (γ-glutamic acid) hydrogels as tunable scaffolds for stem cells differentiation. Carbohydr Polym. 2021; 264 (1-3), 118048. doi: 10.1016/j.carbpol.2021.118048

Биоматериалы в трехмерной клеточной культуре: регенерация кости и хрящей

Мехмет Филизфидан [1,2], Волкан Текин [3], Азуман Езен [4]

[1] Институт стволовых клеток, Междисциплинарный отдел стволовых клеток и регенеративной медицины, Университет Анкары, Анкара, Турция
[2] Факультет медицины, отдел медицинской биологии, Университет Сельджук, Конья, Турция
[3] Отдел физиологии, Школа медицины Гюльхане, Турецкий университет наук о здоровье, Анкара, Турция
[4] Ветеринарный факультет, Отдел гистологии и эмбриологии, Университет Анкары, Анкара, Турция

Резюме

Клеточные культуры, применяемые для изучения и оценки активности микроокружения в живых организмах на клеточном уровне, были разработаны на основе различных моделей и со временем внесли значительный вклад в исследования. В связи с недостаточной поляризацией, пролиферацией и развитием внеклеточного матрикса клеток в двумерных (2D) культурах, ведущих к ограничению таких прижизненных клеточных функций, как их морфология, нишевая роль в микроокружении, дифференцировка, пролиферация, метаболизм препаратов, жизнеспособность, продукция матрикса, экспрессия генов и белков, повысился интерес к трехмерным (3D) культуральным моделям. В данной обзорной статье мы обсуждаем важность трехмерных культур клеток и даем общее представление о свойствах биоматериалов, применяемых для конструирования 3D-несущих структур и их взаимодействий с клетками.

Ключевые слова

Биоматериалы, кость, хрящ, регенерация, клеточная культура, внеклеточный матрикс, стволовые клетки.