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PREFACE

Advanced 3D Cell Culture Platform for Tissue Engineering

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In recent decades, the development and application of cell culture platforms has emerged as a promising interdisciplinary field to address critical challenges in tissue engineering and regenerative medicine. By integrating principles from biology, engineering, and materials science, remarkable progress has been made in the development of functional tissue constructs for various applications. One of the major advantages of three-dimensional (3D) cell culture platforms lies in their ability to recapitulate the structure and biological microenvironment of living tissues, thereby better representing in vivo conditions compared to conventional two-dimensional (2D) culture methods. In this special issue, we aim to explore the latest advances, challenges, and future perspectives in the field of 3D cell culture for tissue engineering.

I am pleased to present nine articles that discuss advanced 3D cell culture platforms for tissue engineering. These articles cover a wide range of topics, including (1) 3D disease modeling for drug screening, (2) 3D platforms for enhanced therapeutic efficacy, and (3) a novel method for improved tissue preservation. Authored by leading experts in the field, these contributions offer valuable insights into the development and application of various 3D culture platforms, such as spheroids, organoids, scaffolds, hydrogels, bioprinting, and organ-on-a-chip systems.

The first two articles in this special issue focus on advances in 3D cell culture platforms for tissue/disease modeling, addressing the limitations of 2D cell monolayers in accurately representing complex tissue dynamics. These articles highlight the use of hydrogels, scaffolds, 3D printed structures, organs-on-a-chip, and organoids as next-generation platforms that enable drug screening and mechanistic studies for specific diseases. By incorporating 3D physical structure and intercellular interactions, these innovative approaches aim to improve the accuracy and reliability of tissue modeling. In addition, the articles discuss the future prospects and potential impact of these technologies in advancing our understanding of disease mechanisms and facilitating the development of novel therapeutics. Together, these articles provide valuable insights into the state of the art in 3D cell culture platforms, paving the way for next-generation approaches to tissue and disease modeling.

The first article, titled “Tissue-Engineered 3D In Vitro Disease Models for High-Throughput Drug Screening” by Huskin et. al. provides a comprehensive review of various 3D disease models that offer high accuracy for high-throughput drug screening, highlighting the limitations of 2D models in effectively representing complex pathophysiology in cancer and cardiovascular disease [1]. Given the critical role of incorporating multiple factors such as extracellular matrix (ECM)-mimicking biomaterials, diverse cell types, and microfluidic systems in recapitulating complex tissue, the article specifically emphasize the recent advancements in these areas. The incorporation of these factors into 3D cell culture platforms has significant implications for applications such as drug screening.

The second article, titled “Advanced In Vitro Three-Dimensional Skin Models of Atopic Dermatitis” by Jang et. al. provides a comprehensive review of *in vitro* 3D skin models specifically designed to study atopic dermatitis (AD) [2]. Utilizing of human dermal cells, including keratinocytes, dermal fibroblasts, immune cells, endothelial

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cells, and sensory neurons within the platforms such as transwell, organ-on-a-chip systems, and organoids, these in vitro skin models offer a high degree of accuracy in mimicking inflammatory skin diseases. The review explores various approaches such as cytokine treatment, genetic engineering of dermal cells, and co-culture with AD-inducing microbes, which will undoubtedly captivate readers interested in skin diseases, as well as those exploring the intricacies of the skin microbiome.

The following six articles are dedicated to the exploration of various 3D cell culture platforms aimed at enhancing the therapeutic efficacy of tissue regeneration. These articles highlight the remarkable capabilities of 3D platforms to faithfully replicate the intricate microenvironment of natural tissues, thereby stimulating cells and enhancing the potential of cell-based therapies. Cells cultured under 3D conditions exhibit enhanced cell-to-cell or ECM-to-cell communication, which in turn promotes cellular activation, induction of differentiation, or increased secretion of paracrine factors. Thus, the fabrication of 3D cell aggregates and the development of 3D scaffolds with innovative technologies are rapidly emerging as potent tools in the field of regenerative medicine.

The third article, titled "Three-Dimensional Cell Culture System for Tendon Tissue Engineering" by Son et al. [3] provides a comprehensive review of the advances in in vitro tendon mimetic scaffolds reconstituted using 3D cell culture systems. Tendon injuries represent a significant challenge due to their limited regenerative capacity and therapeutic options, highlighting the indispensability of cell therapy. This review explores the various strategies used for tendon tissue engineering and their applications in preclinical studies, with a particular emphasis on tendon regeneration. 3D platforms such as cell spheroids and cell-laden scaffolds with or without the use of bioprinting technology are presented in this article, which provide valuable insights into ongoing efforts to improve tendon regeneration through tissue engineering approaches.

The fourth article, titled "Acoustic and Magnetic Stimuli-Based Three-Dimensional Cell Culture Platform for Tissue Engineering" by Seo et al. [4] provides a comprehensive review of advanced techniques for synthesizing 3D cell aggregates using physical stimulation, especially acoustic or magnetic stimuli. The article highlights the ability of these methods to rapidly generate spheroids, 3D network structures, and cell sheets, while effectively regulating stem cell differentiation and paracrine factor secretion. With the potential to outperform conventional approaches in terms of productivity and cost-effectiveness, the use of acoustic and magnetic stimuli-based techniques in 3D cell culture holds promise as a next-generation method in the field of tissue engineering.

The fifth article, titled "Development of Hetero-Cell Type Spheroids via Core-Shell Strategy for Enhanced Wound Healing Effect of Human Adipose Derived Stem Cells" by Lee et al. [5] proposes a novel approach to improve the therapeutic efficacy of human adipose-derived stem cells (hADSCs) in wound healing by producing a core-shell structured spheroid consisting of a central aggregation of hADSCs surrounded by human dermal fibroblasts (hDFs). Compared to randomly mixed hADSC-hDF spheroids, this core-shell structure exhibits superior wound healing properties, including enhanced cell survival and increased release of angiogenic growth factors. This innovative heterotypic cell co-culture system introduces a novel mechanism of intercellular interaction critical for tissue regeneration.

The sixth article, titled "The Effect of the Mechanical Properties of the 3D Printed Gelatin/Hyaluronic Acid Scaffolds on hMSCs Differentiation towards Chondrogenesis" by Choi et al. [6] presents a novel 3D printed hydrogel scaffold made of gelatin and hyaluronic acid, which specifically promotes chondrogenic differentiation of human mesenchymal stem cells (hMSCs). It has been widely reported that the mechanical properties of the surrounding biomaterial play a critical role in controlling the fate of hMSCs when cultured in 3D. In the case of hydrogels, the degree of cross-linking can be manipulated to control these mechanical properties. The results presented in this study show that a scaffold with a Young's modulus of 25.79 kPa maximizes chondrogenesis, as evidenced by the expression of key genetic markers associated with chondrogenic differentiation.

The seventh article, titled "Breast Tissue Reconstruction Using Polycaprolactone Ball Scaffolds in a Partial Mastectomy Pig Model" by Shim et al. [7] proposes a novel 3D approach to breast tissue reconstruction after mastectomy. The study presents a 3D-printed polycaprolactone (PCL) ball-type scaffold with a collagen coating. The PCL balls, designed in a zigzag pattern, which inherently exhibit excellent flexibility, were coated with collagen to enhance biocompatibility, increase type I and type III collagen deposition, and reduce inflammatory responses. Together, these factors promote in situ infiltration of adipose tissue and fibroglandular tissue when transplanted in vivo, compared to bare PCL scaffold. Although the study focuses primarily on the transplantation of cell-free scaffold, the potential application of this proposed 3D platform for cell transplantation holds great promise for the future research and clinical applications.

The eighth article, titled "Various Three-Dimensional Culture Methods and Cell Types for Exosome Production" by Lee et al. [8] provides a comprehensive review of the use of 3D culture platforms to improve and optimize exosome production. While exosomes have gained

significant attention in recent years as one of the most potent therapeutic tools, their low productivity relative to therapeutic dose poses a challenge requiring the development of novel exosome production systems. This article presents exosome-producing bioreactors that incorporates 3D culture platforms such as spheroids, hydrogels, or hollow fibers, providing an enhanced microenvironment for the exosome-secreting cells, resulting in increased yield and functionality. This approach suggests a novel paradigm for the collection of therapeutic exosomes with potential applications in multiple interdisciplinary fields.

The ninth and last article, titled "Role of Klotho and N-acetylcysteine in Oxidative Stress Associated with the Vitrification of Ovarian Tissue Cytoprotective Function of Klotho in Cryopreservation" by Kim et al. [9] proposes N-acetylcysteine and Klotho as novel candidates for cryoprotective molecules to mitigate damage to frozen cells or tissues, particularly in terms of preserving fertility. Both biomolecules were found to induce tissue vitrification and effectively down-regulate oxidative stress during the freezing process. In contrast to conventional dissociated cell preservation methods, which often overlook the importance of ECM compounds and cellular interactions, these novel insights into the preservation of 3D cell aggregates or tissues provide valuable contributions to the fields of drug screening and cell therapy.

The articles presented in this special issue cover a wide range of topics, including 3D disease modeling for drug screening, improved therapeutic efficacy of cell-based therapies, and tissue preservation, by the incorporation of 3D physical structures, intercellular interactions, and ECM-mimicking biomaterials. These 3D cell culture platforms exhibit promising results in improving the accuracy and reliability of tissue models, resulting in enhanced tissue regeneration, cell differentiation, and exosome production. These novel insights and techniques provide valuable contributions to the fields of tissue regeneration and regenerative medicine and will pave the way for future research and advancements in these fields, ultimately leading to improved clinical outcomes and patient care. We hope that this special issue will serve as a valuable resource for researchers, clinicians, and professionals working in the field, fostering further advances and collaborations in the exciting realm of 3D cell culture for tissue engineering.

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