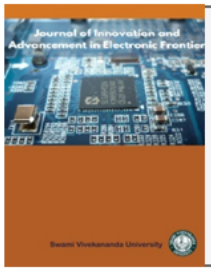
Journal of Innovation and Advancement in Electronic Frontier, *Volume 1 (Issue 1: June, 2024), Pages 21- 25*
Published on:1st July,2024



Journal of Innovation and Advancement in Electronic Frontier

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ECIS-Based 3D Cell Growth Analysis: Real-Time Monitoring of Cellular Dynamics

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Abstract

The study of three-dimensional (3D) cell growth has gained significant attention due to its closer resemblance to in vivo conditions compared to traditional two-dimensional (2D) cultures. Electric Cell-Substrate Impedance Sensing (ECIS) provides a real-time, label-free method to monitor cellular behavior, including proliferation, adhesion, and morphological changes. This paper explores the application of ECIS technology in assessing 3D cell growth, emphasizing its advantages, limitations, and potential applications in biomedical research and drug discovery.

Keywords: *ECIS, 3D cell culture, Impedance measurement, Real-time monitoring, Drug discovery.*

1. Introduction

The traditional 2D cell culture model has long been the gold standard for in vitro studies; however, it fails to recapitulate the intricate cellular interactions and microenvironment of living tissues [1]. The emergence of 3D cell culture models has provided more physiologically relevant systems for studying cellular dynamics [2]. A 3D cell culture biochip has been introduced for integrating the electrical impedance measurement system for quantifying the cell count in the 3D cell culture structure. The perfusion 3D cell culture and detection of cell concentration in 3D culture environment have been shown in Figure 1 [3].

ECIS is a non-invasive technique that enables real-time monitoring of cellular activities, including barrier function, motility, and proliferation [4]. ECIS has been widely used in 2D cell cultures, and its application in 3D models presents an innovative approach to studying cell growth dynamics. Oliveira et al. reviewed on leveraging existing 3D cell culture systems combined with integrated electrochemical sensing for potential use in cancer models, aiming to improve diagnosis and treatment [5]. Also, Yalcin et al. surveyed on innovative electrical measurement methods introduced in the literature for the analysis of 3D cell cultures [6].

This paper evaluates the principles of ECIS, its integration into 3D cell cultures, and its implications for biomedical research.

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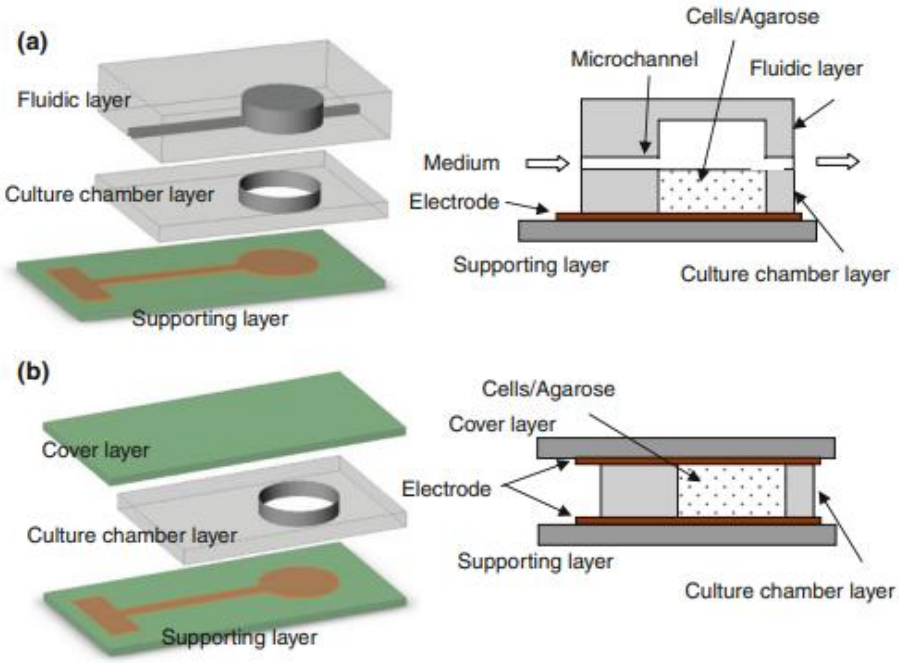

Figure 1 (a) Illustration of the biochip for performing perfusion 3D cell culture. (b) Illustration of the biochip for detecting cell concentration in 3D culture environment (Adapted from Ref. [3])

2. Principles of ECIS Technology

ECIS is based on the measurement of impedance across a substrate containing electrodes in the presence of cells. The impedance is influenced by cellular behaviors such as adhesion, spreading, and barrier formation [7]. When cells proliferate and cover the electrode surface, they modulate the impedance, providing insights into their growth patterns and interactions [8]. The application of ECIS in 3D cell cultures requires adaptations in electrode design and positioning to accommodate the spatial complexity of 3D cell structures [9].

3. Application of ECIS in 3D Cell Growth Studies

Integrating ECIS into 3D cell cultures requires specialized electrode configurations that enable impedance measurements across multilayered cellular structures [10]. Studies have demonstrated that ECIS can effectively monitor cell adhesion, proliferation, and differentiation in 3D spheroid models [11]. By placing electrodes at different depths within a scaffold, researchers can assess the dynamic changes in cellular interactions within the 3D environment [12]. The use of biomimetic scaffolds, such as hydrogels and extracellular matrix (ECM) analogs, further enhances the physiological relevance of these models [13]. A microgroove impedance sensor has been specifically designed for the real-time, noninvasive monitoring of cell viability in 3D cultures. The conventional EIS method for monitoring 2D cell viability relies on the attachment of cells to the sensor surface. However, 3D cells are encapsulated and cultured in Matrigel, which hinders their attachment and movement. As a result, this study discusses the 3D ECIS principle for monitoring 3D cell cultures. The schematic diagram of 3D cell sensing and detection has been shown in Figure 2 [14].

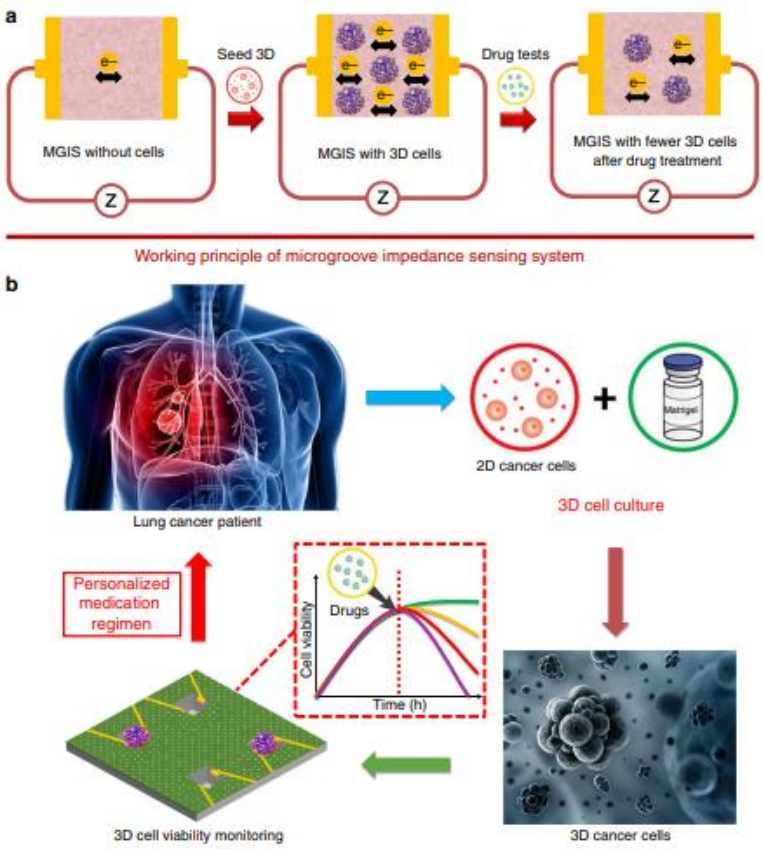

Figure 2 Schematic illustration of 3D cell sensing and detection. a The working principle of 3D ECIS: the number of living cells influences the conductivity of the Matrigel/cell construct. b Schematic of the 3D ECIS for antineoplastic drug screening (Adapted from Ref. [14]).

4. Advantages and Limitations of ECIS in 3D Cell Cultures

ECIS offers several advantages for studying 3D cell growth. It provides real-time, quantitative data on cellular behaviors without the need for exogenous labels or destructive endpoints [15]. Additionally, ECIS allows for high-throughput screening, making it valuable for drug discovery applications [16]. However, challenges remain, including the complexity of electrode design for 3D environments and the need for standardization across different cell types and culture conditions [17]. The interpretation of impedance signals in a 3D setting is more complex than in 2D due to additional factors such as scaffold conductivity and cell layering effects [18].

5. Implications for Biomedical Research and Drug Discovery

The application of ECIS in 3D cell cultures holds great promise for various biomedical fields. In cancer research, ECIS can be used to study tumor spheroid growth, invasion, and response to therapeutics [19]. The technology also has applications in tissue engineering, where it can monitor cell differentiation and scaffold integration [20].

Furthermore, ECIS-based assays offer a high-throughput platform for screening drug candidates in physiologically relevant 3D models, potentially improving the predictive accuracy of preclinical studies [21].

6. Conclusion

ECIS represents a powerful tool for monitoring 3D cell growth in real-time, offering numerous advantages over traditional microscopy-based methods. Its non-invasive nature and ability to provide continuous measurements make it particularly suited for studying dynamic cellular processes. Despite the challenges associated with adapting ECIS to 3D models, ongoing advancements in electrode design and data interpretation are likely to enhance its utility. The integration of ECIS into 3D cell culture systems has the potential to revolutionize in vitro modeling for biomedical research and drug discovery.

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