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Popular Article

Organoids in Drug Discovery: A Transition from 2D to 3D cultures

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Abstract

The drug development process is extensive and costly mainly due to the frequent disparity between the promising lead compounds pinpointed in laboratory conditions and their ability to generate analogous effects within living organisms. The domain of drug discovery is continually evolving, steered by a variety of creative methodologies and technological advancements like Artificial Intelligence (AI) and Machine Learning, Immunotherapy, CRISPR Technology, Organoids and 3D Cultures, Drug Repurposing, Biological and Targeted Therapies, Biotechnology, Proteomics and Metabolomics, Microbiome Research, Drug Delivery Systems. Some of these innovative techniques such as Organoids and 3D cultures offer a biologically realistic foundation for evaluating potential drug candidates. Organoids are intricate three-dimensional tissue constructs that originate from stem cells and closely resemble the organization and functionality of particular human organs or tissues. Their value in drug discovery and advancement is substantial because they offer a more precise representation of human biology in contrast to conventional cell cultures or animal models. Recent studies have proven the successful application of organoids for identifying precision medicine for colorectal cancer, cystic fibrosis, pancreatic ductal adenocarcinoma, and neurodegenerative disorders.

Introduction

Drug discovery is currently facing a critical juncture. Although there is a growing trend of creating extensive and diverse collections of compounds for initial screening, the potential benefits of the lead compounds that are identified in these screens often go largely unfulfilled. Drug development is a lengthy and expensive process primarily because there is often a lack of consistency between the promising lead

compounds identified in laboratory settings and their ability to produce similar outcomes in living organisms. The landscape of drug discovery is continuously changing, driven by a range of innovative strategies and advancements in technology. Some of the latest trends and approaches in drug discovery include Artificial Intelligence (AI) and Machine Learning, Immunotherapy, CRISPR Technology, Organoids and 3D Cultures, Drug Repurposing, Biological and Targeted Therapies, Biotechnology, Proteomics and Metabolomics, Microbiome Research, Drug Delivery Systems. Some of these innovative techniques such as Organoids and 3D cultures offer a biologically realistic foundation for evaluating potential drug candidates.

An organoid is a miniature assembly of cells thriving within a carefully designed 3D milieu. In this environment, these cells exhibit self-organization and specialize into fully functional cell types, faithfully mimicking the structure and function of a living organ, hence earning the nickname "mini-organs" (Huch and Koo, 2015). Organoids can be created using embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), or stem cells derived from neonatal or adult sources (ASCs) (Lancaster and Knoblich, 2014). Within organoids, self-organization takes place as a result of constrained lineage commitment and the sorting of cells in specific spatial arrangements. This process is driven by the activation of various signaling pathways, which can be influenced by intrinsic cellular elements or external factors such as the extracellular matrix (ECM) and the culture medium (Corro *et al*., 2020). The precedence of using organoids as a research model way back to 2011, based on a PubMed literature search conducted by Simian and Bissell (2017), there has been a significant surge in the number of publications incorporating the keyword "organoids" since 2011. This demonstrates the dynamic growth of research in the field of organoid models. Organoids offer an entirely novel research model for medical studies, encompassing histopathology, drug development (Fong *et al*., 2018), and precision medicine (Pauli *et al*., 2017). Nevertheless, in contrast to the well-established traditional approaches of using cell lines, xenograft and animal models in research and practical applications for many decades, the concept of organoids remains relatively unfamiliar to numerous researchers, and this model is still in the early stages of development.

Historical Landmarks

The field of organoids is a relatively recent area of research, but it has been rapidly progressing and has significantly contributed to our knowledge of human biology and diseases. The use of cell cultures began in the early 20th century, with researchers culturing cells in 2D environments. While this was a significant step in understanding cellular biology, it lacked the complexity of three-dimensional tissue structures. Early attempts at 3D cell culture techniques emerged in the 1907, when Van Peters did the earliest effort at regenerating organisms in a controlled environment. He illustrated that individual sponge cells, when separated, have the capacity to autonomously reassemble and regenerate an entire organism. but these were often limited in terms of complexity and lacked the sophistication of modern organoid culture method. The year 1981 marked a significant milestone in stem cell research when pluripotent stem cells (PSCs) were first identified and extracted from mouse embryos. This breakthrough provided a substantial impetus for further exploration in the field of stem cell research (Martin, 1981). Towards the

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end of the decade, the creation of induced pluripotent stem cells (iPSCs) from both mouse and human fibroblasts became possible through reprogramming. This breakthrough has had a profound influence on the realms of stem cell and organoid research (Takahashi *et al*., 2007). The transition in organoid research from two-dimensional (2D) to three-dimensional (3D) occurred when Eiraku and colleagues (2008) managed to generate cerebral cortex tissue from embryonic stem cells (ESCs) through the utilization of a 3D aggregation culture technique. In 2009, Sato and co-workers achieved a significant breakthrough by demonstrating the creation of 3D intestinal organoids. They achieved this by utilizing a single leucine-rich repeat-containing G protein-coupled receptor 5 (Lgr5) expressed in adult intestinal stem cells, embedding them in Matrigel, which is an extracellular matrix (ECM). Notably, these 3D intestinal organoids exhibited the ability to self-organize and differentiate into a structure resembling the crypt-villus structure without the need for a mesenchymal niche. This ground breaking work served as a catalyst for subsequent research in other organ systems, including those of mesodermal origin (such as the stomach, liver, pancreas, lung, and kidney) and neuroectodermal origin (such as the brain and retina) (Figure1).

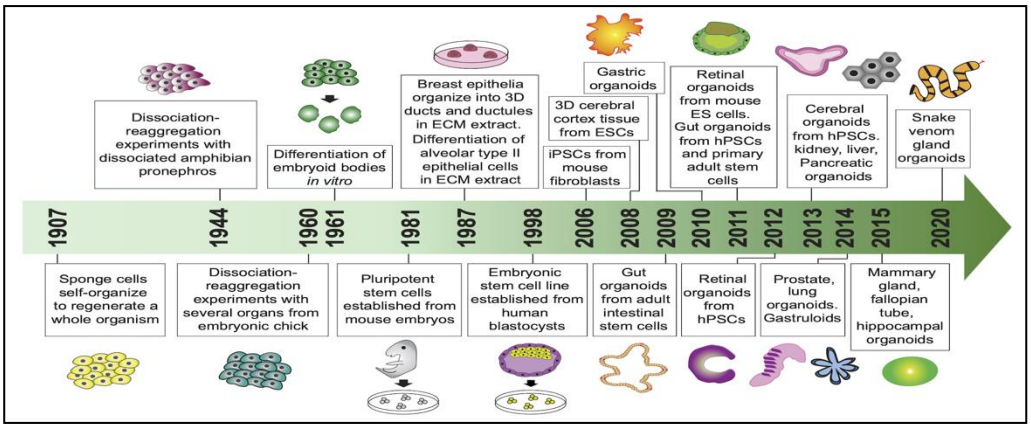

Figure 1: Timeline of the key landmark studies for development of organoid cultures (Corro *et al*., 2020)

Applications of Organoids

Organoids are rapidly gaining prominence as a fundamental tool in numerous biomedical research endeavours. Their extensive applicability, which stems from their ability to represent diverse tissue types, facilitate long-term growth, and replicate the intricate 3D structure found in natural organs, positions them as a ground-breaking technology with myriad biological and clinical uses. Particularly, organoids are widely adopted in applications related to disease modeling, biobanking, precision medicine, and regenerative medicine (Figure 2).

Case studies highlighting role of organoids in drug discovery

Recently developed medical therapies for human ailments often come with challenges, including patient-specific variations, the complexity of forecasting results, and protracted drug evaluation processes.

Organoid cultures tailored to a particular disease and potentially to an individual are anticipated to evolve into robust instruments for precise medical treatments (Walsh *et al*., 2016).

Cancers, infectious ailments, and developmental disorders can be recreated using patient-derived ex vivo biopsy samples, as demonstrated by the existence of biobanks containing colon cancer organoids and

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intestinal organoids from cystic fibrosis (CF) patients. These living clinical specimens have the potential to be valuable for drug testing, genetic editing, or investigations into patient prognosis (Dekkers *et al*., 2016). A study to establish the feasibility of the concept was conducted using a colon cancer biobank, in which 83 drugs that are presently employed in clinical practice or are being evaluated in clinical trials were assessed for their potential as cancer therapies.

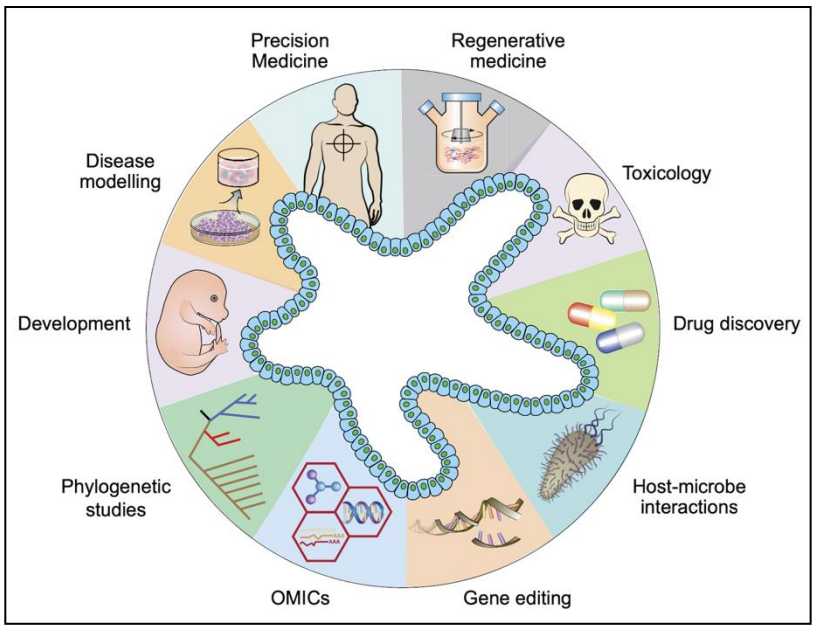

Figure 2: Applications of organoids in various fields (Corro *et al*., 2020).

This screening process confirmed established relationships between genes and drugs, providing evidence that organoid biobanks can be effectively employed for high-throughput screening (Bartfeld and Clevers, 2017).

Apart from the aforementioned study, a separate research effort was carried out to enhance drug development for cystic fibrosis (CF). CF is a condition resulting from particular mutations in the CFTR gene, which ultimately hinder the CFTR protein's placement on the cell's outer membrane. The presence of CFTR at the cell's outer membrane is crucial for maintaining the balance of fluids and electrolytes, and its absence leads to the build-up of thick mucus in the gastrointestinal and respiratory systems. Individuals may experience enduring lung infections, lack of pancreatic function, malnourishment, and a restricted lifespan. In this investigation, Dekkers and co-workers (2013) cultivated organoids from rectal biopsy samples taken from two patients. By conducting a forskolin-induced swelling assay, they determined that the drug ivacaftor (the generic form of Kalydeco) elicited a favorable response. Subsequently, both patients were treated with ivacaftor, resulting in significant improvements in their conditions (Dekkers *et al*., 2016). Adopting a similar method, researchers employed organoids derived from primary human pancreatic ductal adenocarcinoma (PDAC) to pinpoint novel and efficient drugs. These tumor organoids displayed comparable histological characteristics and levels of differentiation markers to the original tumor (Nielsen *et al*., 2016).

In a prior investigation, researchers developed patient-derived organoids from glioblastoma

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(GBOs) to replicate the diversity seen in glioblastoma tumors. They illustrated the effectiveness of GBOs in evaluating personalized treatment approaches by associating the mutational profiles of GBOs with individual drug responses and by simulating chimeric antigen receptor T cell immunotherapy (Jacob *et al.*, 2020).

Conclusion and Future directions

Organoids can be grown in quantity to supply sufficient material for experimental investigations and can be used with a broad spectrum of standard laboratory techniques. This versatility renders organoids an exceptionally encouraging resource for medical research. Currently, organoids are making substantial contributions to fundamental research in areas like developmental biology, adult stem cell biology, and disease modeling. On the clinical front, their most immediate influence is evident in drug screening and the customization of medical treatments. Organoids have emerged as a revolutionary instrument in the realm of drug discovery. They offer a higher level of physiological relevance, facilitating the exploration of diseases, drug reactions, and personalized medicine in unprecedented ways. Organoids have effectively served as models for a diverse array of diseases, as well as for drug candidate screening, contributing significantly to our comprehension of intricate biological processes. While organoids have shown great promise in drug discovery, they come with several shortcomings like heterogeneity, standardization, quality control, limited vascularization, lack of immune system interactions, also lacks the complexity of multicellular interaction. Despite these challenges, ongoing research and advancements in organoid technology aim to address these issues and further enhance their utility in drug discovery and medical research. In the near future, kidney and liver organoids may serve as valuable additions to, or potentially even substitutes for, the present animal testing methods used to assess toxicity.

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