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Emerging of Three-Dimensional Models To Study Human Diseases

EDITORIAL

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For several decades, biomedical research has traditionally relied on the use of two-dimensional (2D) cell culture and animal models to study human biology and diseases. However, it can be difficult to address questions that are relevant to human biology and diseases in animal models or 2D cell culture, such as genetics, development, immune response, and cell host tropism. Furthermore, scarcity of advanced *in vitro* and *in vivo* models has hindered progress in understanding disease causes and, as a result, the creation of innovative therapeutic methods for patients. To improve our understanding and the current situation, more physiologically and realistic research models for mechanism-based target identification, drug development and screening, developmental biology, cancer and infectious diseases are needed. Historically, disease mechanisms in animal models have been studied using a common discovery pipeline, in which biological processes were first probed using genetic screening in invertebrates, then in mammalian model systems, and finally clinical translation to humans (Denayer, et al. 2014). It is worth mentioning that this approach has led to a deep mechanistic knowledge of many human disorders. However, a variety of biological processes that are unique to humans can not be replicated in animal models or immortalized cell lines completely. Because of human-specific developmental events and mechanisms. In addition, human physiology differs significantly from that of the mouse model system, given that humans develop much more slowly than the animal models. It is perhaps expected that there are significant disparities in metabolism between humans and laboratory animals. Importantly, humans are not inbred, unlike all other animal models. Understanding human genetic variability and its impact on disease onset, development, and drug responses is essential for designing individualized medical therapies, and it necessitates the creation of human specific model systems (Tiriac et al. 2019; Haffter et al. 1996). Modeling human biology and diseases *in vitro* has been advancing during the last decade, particularly the production of the three-dimensional (3D) organoids from different human tissues. These organoids can be made from biopsies extracted directly from the organ of interest or from sick patient tissue. These stem-cell-derived self-organizing tissues offer a unique system for studying mechanisms spanning from organ development, cell signaling, genetics, modeling cancer, drugs and therapeutics screening, and studying infectious disease (Schlaermann et al. 2016; Lancaster et al. 2019; Kretzschmar et al. 2016). This is because the tissue morphology, cell-cell interaction and signal transduction in human 3D organoids resemble the human architecture and signaling events *in vivo*. In addition, organoids develop according to their own developmental programs *in vitro*. Further, 3D organoids are becoming fundamental in personalized medicine, because they can be produced from human progenitors, to study processes and diseases that are unique to the donor. Finally, even with additional advancements, 3D organoids will not be able to replace existing models and should be viewed as a supplement to other approaches. For example, 3D organoids can not replace animal models since the *in vivo* whole organism is still required when screening for drugs or therapeutics (Nusslein-Volhard 2012; Brenner 1974; Kostic et al. 2013).

In addition to human adult stem cell cultivation methods, 3D organoids, human induced pluripotent stem cell (iPSC) technology have made it possible to

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create laboratory models that are unique to an individual (Xiang et al. 2017).

Exposure of iPSCs to a series of differentiation stimuli enables the differentiation of iPSCs into one kind of cell and their cultivation in 2D. More recently, the differentiated iPSCs clump together to form an organ bud. This culture method has been devised to simulate *in vivo* organ development in 3D, allowing for the simultaneous modeling of more complex tissue architectures and different cell types (Takahashi et al. 2007). This in turn recapitulates the mature organ structure *in vitro*. Although reprogramming other cells into iPSCs has become a common laboratory operation, creating disease models from such cell lines is still difficult. However, extrapolating results from model systems to humans has become a major bottleneck in the drug discovery process. In addition, current research has uncovered biochemical processes unique to the human body that can not be replicated in other animal models. iPSC, once established from a patient, can be used to repeatedly generate different tissue models without any time limit unlike the 3D organoids which requires access to tissue and prior knowledge of the culture conditions for that tissue which might limit the establishment of human 3D organoids. In addition to 3D organoids and iPSC, attempts to model the biology of human organs using bioprinting of human cells; and cell culture in a microfluidic device, had shown some promise for drug screening, toxicity and human disease research *in vitro*. These cutting-edge technologies could help scientists better understand normal human organ function and disease pathology, as well as forecast the safety and efficacy of experimental medications and therapeutics in humans. As a result, these new technologies are expected to be beneficial supplements to standard preclinical cell culture methods and *in vivo* animal research models in the near future, and possibly even replacements in the long run (Schmidt et al. 2020; Rossi et al. 2018). As a result, the emergence of human *in vitro* 3D cell culture systems using stem cells from various organs has gotten a lot of interest as a way to overcome these restrictions. For example, human 3D organoids, which are 3D culture systems produced from stem cells, have made it possible to re-create the design and physiology of human organs in astonishing detail. Human organoids complement animal models and give unique opportunities for the study of human disease. Through the genetic engineering of human stem cells, as well as directly when 3D organs are created from patient biopsy samples, together with technological advancements, these provide a series of powerful and efficient platforms for researching human development, physiology, infectious diseases, genetic abnormalities, and malignancies.

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