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Current Opinion in Biomedical Engineering

The future of biomedical engineering: Bioengineering of organoids and tissue development

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Current Opinion in Biomedical Engineering 2020, **13**:A1–A2

This review comes from a themed issue on **Futures of Biomedical Engineering: Bioengineering of Organoids and Tissue Development**

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https://doi.org/10.1016/j.cobme.2020.07.002

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Dr. Fu is a Full Professor of Mechanical Engineering at the University of Michigan, Ann Arbor. His group integrates micro/nanoengineering, single-cell technologies, and systems and synthetic biology methods with new discoveries of mechanobiology, epigenetics, and stem cell biology for advancing understandings of human development and cancer biology. Dr. Fu's research on developing synthetic models of human embryonic development has contributed significantly to the emerging field of 'Synthetic Embryos', which was selected by the *MIT Technology Review* as '10 Breakthrough Technologies of 2018'.

The future of bioengineering for multicellular organoids and tissue models has never been brighter. Such organoids and tissue models are organized multicellular constructs that replicate the key structural and functional characteristics of their *in vivo* counterparts. Through a decade of research, organoids and tissue models including those mimicking the brain, retina, intestine, kidney, and liver have been developed. These synthetic multicellular models are emerging as a promising approach for the modeling of development, homeostasis, and disease of various human organs and tissues.

Conventional methods of forming organoids and tissue models rely on three-dimensional (3D) cell culture. Although simple and widely adopted, the current 3D culture techniques suffer from limited controllability, reproducibility, and efficiency due to a lack of engineering control of environmental signals including both cell–cell and cell–matrix interactions. Advanced bioengineering tools that can dynamically control the cellular environment to provide instructive signals have the potential for significantly improving the controllability and reproducibility of these multicellular models.

The articles in the issue cover the latest bioengineering advances in human embryo models (or embryoids), kidney organoids, tumor organoids including glioblastoma multiforme (GBM) models, models of neurological disorders, and computational methods for organoid systems. This issue also includes reviews on the engineered extracellular matrix (ECM) for epithelial morphogenesis and engineering principles, challenges, and opportunities relevant to organoids and tissue models.

Hadjantonakis et al. [1] review the recent advance of synthetic embryology. Over the last few years, scientists have endeavored to use mammalian stem cells to generate embryoids *in vitro* to recapitulate the first few days of mammalian development. Synthetic embryology enables mechanistic investigations of molecular and cellular dynamics driving embryogenesis without using intact embryos, thus promising for advancing knowledge of human development, particularly at the postimplantation stages. Future advance of synthetic embryology hinges on a deeper understanding of the developmental state and potency of stem cells used in embryoid models, as well as incorporating bioengineering tools to control cell–cell interactions and their assembly processes.

Along a similar line, Xue et al. [2] provide a review of models of early human neural development. Using bioengineering tools, different aspects of regional patterning of the ectoderm and of the neural tube have been

recapitulated in embryoid models. Xue et al. [2] further discuss future opportunities to apply bioengineering tools to control neural tissue morphology and architecture, morphogen dynamics, intracellular signaling events, and cell–cell interactions for further development of these models and their applications.

Offeddu et al. [3] review models of neurological disorders for quantifying drug distribution, engagement, and function, particularly those related to vascular barriers in neurological conditions. The balance between complexity and high throughput of these models is an important consideration affecting their adoption in the industry and the clinic. Patient-specific models of neurological conditions have started to emerge, promising for future personalized medicine.

In vitro 3D tumor models have been an important means to understand tumor biology. A wide range of 3D tumor models have been developed allowing identification of the role of the tumor stroma and tumor interactions with surrounding tissues [4]. Organoids developed from cancer stem cells or patient-derived xenografts represent an opportunity to better understand how tumors evolve and develop targeted therapies [4]. Silvia and Dai [5] review GBM models in which GBM tumor cells have been incorporated into cerebral organoids. Although the current GBM-incorporated cerebral organoids remain suboptimal for mechanistic investigations, due to their limited controllability and reproducibility, they are starting to show promise for investigating GBM invasion and its effect on the brain ECM.

Kidney organoids have shown great promise for nephrotoxicity screening and modeling of kidney development and renal diseases. Takasato and Wymeersch [6] review the current status of kidney organoids and their immediate basic and translational applications. Further development of kidney organoids will focus on their limitations, including a lack of cell maturation, limited cell diversity, vascularization, and functionality.

The ECM is an important component for multicellular development and assembly. Nerger and Nelson [7] discuss engineered models of the native ECM and their applications for studies of epithelial morphogenesis. Albeit challenging, ongoing efforts are directed to reproduce the structural and molecular complexity of the native ECM in synthetic models. Engineered models of the native ECM will enable further investigation of the dynamic mechanisms underlying cell–ECM interactions and their roles in tissue morphogenesis and patterning.

An ongoing challenge in the organoid field has been to control the organoid development to produce highly reproducible structures. Such reproducibility is essential to faithfully model developmental pathways, create tissues for implantation, and develop high throughput screens for drug development. Norfleet et al. [8] summarize the mechanistic and machine learning models being used to increase our understanding of organoid development. These models are at an early stage, and future models need to incorporate metabolic and biophysical phenomena.

As the field of organoids and tissue models moves forward, discussions of the standardization and benchmarks of these models become necessary. Hinman et al. [9] discuss the engineering benchmarks and principles identified to guide the construction of multicellular organoid and tissue models. Importantly, the applications and challenging or problematic aspects of multicellular organoid and tissue models as a potential regulatory tool are reviewed. Matthys et al. [10] focus on discussing technical challenges to identify the critical starting parameters for organoid reproducibility, systematically manipulate the proportions of differentiated cells from progenitors, and comprehensively characterize cell phenotypes spatially. Incorporation of bioengineering tools, including advanced imaging and spatial transcriptomics, will undoubtedly improve the robustness and predictability of organoid and tissue models.

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