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LETTER

Synthetic morphogenesis: why reverse engineering should be prioritized

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Dear Editor,

In morphogenesis, the sequential execution of tissue arrangement depends on a vast array of signaling proteins and cellular response. Several mechanisms of such response have been identified: apoptosis, proliferation, fusion, adhesion, sorting, transition, folding, migration and expansion. Different combinations of these responses lead to the formation of various anatomical structures [1, 2].

Synthetic morphogenesis aims to explore specific aspects of natural morphogenesis and reproduce them in experiment [3]. Existing technological foundations have been focused on specific signaling pathways and response mechanisms. As such, progress in engineering of human organs and complex tissues has been slow, and it is now time to base further development on the mechanisms of in vivo morphogenesis. 'Reverse engineering' can help mimic the in vivo processes to increase the success rate of synthetic morphogenesis. Morphogenesis is a complex process and includes several components. Undoubtedly, the next step in synthetic morphogenesis should be the unification through reverse engineering of the following achievements:

Self-organizing systems

The idea of utilizing cellular genetic mechanisms for biomimetic recreation in vitro has pushed the exploration of embryoids, organoids and gastruloids as examples of self-organizing complex biological structures. Several studies focused on analyzing the intricate mechanisms regulating the self-organization of these systems: adhesive forces, autocavitation, influence of external mechanical, biochemical signals and morphogen-secreting cells [4, 5]. The ability to reproduce the full specter of regulatory influences ex vivo has yet to be achieved, resulting in creation of unsuitable for in vivo use organ models and scaffolds [6].

Gene regulation influence

Extensive mapping of the genetic code has granted the ability to create gene regulatory networks (GRNs), which serve as control systems for morphogenetic cellular development. Transcription factor (TF)-based engineering has been applied to activate specific GRNs to stimulate spontaneous morphogenesis. Reverse engineering of self-organizing systems has granted the ability to differentiate key TFs and their role in intracellular regulation [7]. Creating a computerized model for calculation of specific algorithms for targeted morphogenesis through genetic circuits seems to be a possible key to synthetic organogenesis. Single-cell analytics and in situ molecular profiling can aid in mapping of developmental GRNs, which will be necessary to fully decode dynamic cell state transitions, and help design functional synthetic circuits [8].

Synthetic promoters

miRNA levels have been shown to differentiate between a wide range of cell types and have been used as classifiers for certain cell populations [9]. Stratification of knowledge on miRNA-responsive sensors allows for creation of a functional database which can serve as a guide to using synthetic promoters for morphogenetic stimulus [10]. Existing genome targeting tools (transcriptor activator-like effectors, CRISPR-Cas9 system and zinc finger proteins) offer the

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ability to develop specific GRN activation or suppression [11, 12].

Molecular engineering

Cellular motility has been shown to respond to influences from intercellular synthetic communicators [13]. Several such systems have been introduced [14–16], yet most lack signal systems found in intracellular signaling events.

Advanced scaffold delivery systems

Building upon existing knowledge of the complex mechanisms behind morphogenesis, several scaffolds have been developed to mimic the highly interconnective cell–ECM environment. 3D-printed modifications of ε-caprolactone scaffolds with microspheres embedded between their fibrils releases microsphere content throughout slow biopolymer degradation over a course of weeks [17]. By modifying the number of embedded microspheres and their contents, it is possible to control the delivery rate of stimulatory factors to growing cells. This partially recreates the capabilities of an extracellular matrix, which influences cellular morphogenesis through varying concentrations of growth factors [18, 19].

Synthetic biology

Current achievements in synthetic biology allow us to understand and partially replicate the mechanisms of complex cellular communication and hierarchy within specialized tissues [20]. Recent achievements in this field open new vistas for the reproduction of tissue-specific functional structures through understanding their responses to external and internal factors [21].

Conclusion

Synthetic morphogenesis represents a field on the verge of outstanding new achievements focused on highly functional artificial bio-design. Existing difficulties and challenges with recreation of signaling mechanisms through bioengineering and biochemical reactivity underline the importance of combining research efforts and unifying an approach to reverse-engineer the complex mechanisms of morphogenesis. We believe this can be achieved by mapping the effects of targeted genetic expression profiles, to pinpoint specific algorithms expressed in natural developmental systems and extrapolate key genetic sequences, essential for morphogenetic manipulation. Therefore, reverse engineering of specific morphogenetic actions from mapped genetic profiles seems to be the most feasible prospect in synthetic morphology and can be achieved with existing technology. The mapping of specific gene expressions is a difficult task, yet achieving it can unify current efforts to discover a standardized approach to organ and tissue biosynthesis.

Author contributions VNN conceived and supervised the study; MYS contributed to methodology and helped in writing—original draft; MYN and MYS investigated the study; all authors contributed to writing—review and editing.

Compliance with ethical standards

Conflict of interest V. N. Nikolenko, M. Yu Nikolayev, and M. Y. Sinelnikov declare that they have no conflict of interest.

Ethical approval This study does not contain any studies with human or animal subjects performed by any of the authors.

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