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Editorial overview: Mammalian synthetic biology: from devices to multicellular systems

Hirohide Saito and Yohei Yokobayashi

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Hirohide Saito

Department of Life Science Frontiers, Center for iPS Cell Research and Application (CiRA), Kyoto University, 53 Kawahara-cho, Shogoin, Sakyot-ku, Kyoto, 606-8507, Japan
e-mail: hirohide.saito@cira.kyoto-u.ac.jp

Hirohide Saito is Deputy Director and Professor at the Center for iPS Cell Research and Application (CiRA), Kyoto University. He received his Ph.D. from the University of Tokyo in 2002. After a postdoctoral appointment at the Japan Foundation for Cancer Research, he has worked as a faculty member at Kyoto University. He is interested in the field of mammalian synthetic biology, cell engineering, and nanobiotechnology. He aims to understand and regulate living systems by developing new technologies.

Yohei Yokobayashi

Nucleic Acid Chemistry and Engineering Unit, Okinawa Institute of Science and Technology Graduate University, Onna, Okinawa 904 0495, Japan
e-mail: yohei.yokobayashi@oist.jp

Yohei Yokobayashi is an Associate Professor at the Okinawa Institute of Science and Technology Graduate University. He received his B.S. and M.S. from the University of Tokyo, and Ph.D. in Chemistry at the Scripps Research Institute. After a postdoctoral appointment at the California Institute of Technology, he worked as a faculty member at the University of California, Davis, until 2015. The focus of his research is to engineer functional nucleic acids for chemical and biological applications.

While the fundamental philosophy may be common, the synthetic biology of mammalian cells and bacterial cells are quite different in practice. Quantitative and qualitative differences in the cellular and genomic structures, gene regulatory mechanisms, epigenetics, and physiology require specialized devices and tools to forward engineer mammalian cells. Fueled by various technical advances over the last two decades (e.g. high-throughput sequencing, genome editing, single-cell omics), the synthetic biology of mammalian cells is becoming increasingly sophisticated in the complexity of the engineered circuits. Such efforts can lead to deeper understanding of the biology unique to higher eukaryotes, such as development and self-organization. The promising clinical prospects in gene and cell therapies may also stimulate research activities with practical implications in the mammalian synthetic biology community.

As is the case with prokaryotes, genetic devices that sense chemical and physical signals, turn gene expressions on or off, perform Boolean logic operations, and control protein signals and cellular functions form the foundation of mammalian synthetic biology. The complexity of mammalian cells presents both challenges and opportunities for mammalian genetic devices. Cella and Siciliano review protein-based devices that respond to molecular signals in mammalian cells. These modular devices include those that exploit proteases that are activated by specific intracellular proteins and release membrane-tethered effector domains as well as engineered transmembrane receptors that detect and transduce extracellular signals. Complementing canonical transcription factor-based switches and these emerging protein-based devices, researchers have taken advantage of the rich RNA-based gene regulatory mechanisms in mammalian cells to design RNA devices that do not involve protein factors. Yokobayashi discusses the recent developments in aptamer-based and aptazyme-based RNA devices (riboswitches) that control gene expressions in mammalian cells in response to small molecules. Nakanishi and Saito also cover RNA devices and circuits that respond to biomolecules, focusing on more biologically relevant signals such as proteins and microRNAs. They also discuss the use of RNA-binding proteins to construct layered logic circuits with RNA-only delivery. These emerging classes of devices will undoubtedly benefit basic research and medical applications that aim to control the phenotype of mammalian cells.

CRISPR-Cas9 has had a profound impact on many research fields, and synthetic biology is no exception, driving the field in a totally new direction. The ability to precisely edit complex genomes is of fundamental importance to the synthetic biology of mammalian cells, and CRISPR-Cas technology has made this task significantly easier. More importantly, CRISPR-Cas technology has stimulated the development of diverse classes of devices and tools for synthetic biology. Kim and Lu review recent developments in such devices in mammalian cells. They highlight new Cas proteins, base editors, and CRISPR-Cas activity regulation. Katayama et al. also discuss recent developments in CRISPR-Cas devices, with more focus on emerging applications. Yachie et al. provide two in-depth overviews of state-of-the-art applications, one for CRISPR-Cas-based evolving DNA barcodes to trace cell lineages and another for CRISPR-Cas-based event recorders that record the temporal evolution of cellular states in DNA. It is clear from these reviews that more exciting applications of CRISPR-Cas technology in mammalian synthetic biology are soon to come.

Mammalian cells differentiate and self-organize into tissues and organs. Engineering these high-order functions and structures is a challenging and fruitful frontier of mammalian synthetic biology. Moreover, such efforts require understanding and engineering cell–cell communications and pattern formations. Toda et al. summarize several key strategies to engineer intercellular communications among mammalian cells, including the SynNotch platform developed by the authors. Ebrahimkhani and Ebisuya discuss the engineering of cell–cell communications to understand and control mammalian development. Synthetic developmental biology not only tests our understanding of complex developmental processes, but it may also have practical implications for future cell therapies.

While the scope of these articles is not meant to be comprehensive, they capture some of the most actively pursued topics in the rapidly evolving field of mammalian synthetic biology. We foresee further advances in technology (devices and tools for mammalian synthetic biology) driving the design and engineering of more complex mammalian systems (e.g. multi-cellular systems and organoids) in the coming years.