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The Innovation Life

From gene editing to cell editing: An emerging technology for synthetic biology

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With the rapid advancement of synthetic biology, there is a growing need to engineer increasingly complex genetic traits involving multiple, poorly understood genetic networks or functions. However, current gene-editing technologies in synthetic biology remain applicable only to relatively well-understood and simple metabolic pathways. Here, we propose cell editing—a technology inspired by endosymbiosis—for implementing complex functions into a host chassis that are currently difficult or impossible to achieve. Interkindom endosymbiosis, evolving at different stages, are widespread in nature. Understanding the principles of endosymbiosis can therefore provide a critical blueprint for cell editing. This foundational approach leverages engineered symbiotic interactions to reprogram cellular functions. Through rational design of engineered donor cells (or "functional shuttles") combined with laboratory adaptive evolution, cell editing aims to achieve radical cellular reprogramming—including trophic shift, reconstruction of core energy metabolism, and even *de novo* functional compartmentalization. Ultimately, this endosymbiotic framework has the potential to pioneer new directions in synthetic biology and cell engineering, enabling modular acquisition of complex traits beyond the reach of current gene-editing tools.

Biotechnological development benefited enormously from breakthroughs in basic research. The use of the current Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) technology in synthetic biology is feasible only if the biological background, such as the metabolic pathway, is well understood, and it only involves a relatively small number of genes whose functions are known. For engineering very complex biological traits or structures, such as enabling a non-photosynthetic cell to perform photosynthesis like cyanobacteria do, this is currently still impossible. Even for nitrogen fixation, for which the pathways and components involved are well understood, making plants use directly atmospheric N_2 remains a dream.[1] Is it then possible to develop technologies that would allow us to endow a cell with new and complex functions such as photosynthesis, nitrogen fixation, or others? What could we learn from nature to think about the future technology for basic biological research and their applications, to fulfill the need to engineer more complex biological traits?

Evolution is not a linear process, characterized by the emergence of complex and novel functions, along with morphological changes. One of the most innovative events is the transition from prokaryotic to eukaryotic cells, following a single symbiotic event between an archaeal Asgard host and its endosymbiotic partner belonging to α-proteobacteria. Over time, the symbiont becomes the organelle, mitochondria, whose function is fully integrated into those of the host cell.[2] While mitochondria originated once with the unique endosymbiosis event occurring about 2 billion years ago, photosynthetic organelles, plastids, observed today in different photosynthetic lineages were the results of multiple endosymbiotic events (Figure 1A).[3]

Compared to the long evolutionary history of organelle biogenesis, many symbionts form a wide range of relationships with their hosts. The associations between the symbionts and their hosts may not necessarily be stabilized, and may represent different evolutionary stages of the organellogenesis process. Sea slugs have evolved a novel host organelle termed "kleptosomes" that can both integrate and sustain photosynthetic activity from sequestered algal chloroplasts and digest them as a nutrient source during extreme starvation.[4] This transient state, balanced between chloroplast preservation and digestion, may reflect an early and labile stage in the evolution of photosynthetic organelles in animals. Furthermore, the nitrogen-fixing cyanobacterium UCYN-A, previously classified as an endosymbiont of the alga *Braarudosphaera bigelowii*, has been identified as a novel organelle termed the "nitroplast".[5] These new findings indicate that the discovery of organelles at different evolutionary stages is still expanding, offering a glimpse into the dynamic process of organellogenesis.

Endosymbiosis can provide host cells with complex and innovative functions derived from a prokaryotic or eukaryotic symbiont. Different stages of endosymbiotic events are widespread in nature, suggesting that a symbiotic association between two partners can be established frequently (Figure 1B). Given that endosymbiosis can confer to a host cell with a complex and functional trait that is difficult or impossible to engineer using currently available technology, endosymbiosis may be viewed as a gateway for developing the technology for cell functional engineering. For ease of understanding, this technology as a whole is referred to "cell editing" in contrast to gene editing which is widely used today. We defined it as an engineering approach based on endosymbiosis. It involves reprogramming donor cells or organelles into functional shuttle that can stably deliver specific traits to recipient cells. This process enables the transfer of traits across species by establishing transient or permanent artificial symbiosis to equip recipient organisms with complex new capabilities beyond natural evolutionary limits. Is it then feasible to establish an endosymbiotic-like relationship between two organisms in a time scale manageable in a research laboratory? This will constitute a major hurdle for the development of the cell editing technology. To validate the principle of cell editing, one may need to manipulate organisms capable of forming endosymbiotic relationships at a large scale, so the technology becomes accessible with a framework applicable to different situations. Again, we may learn from nature for the initial development of cell editing. For example, protists can form a variety of symbiotic relationship with prokaryotic cells, which, combined with the ease of culturing and genetically manipulating these unicellular organisms, makes them attractive models for cell editing research.[6]

To accelerate the success of establishing an endosymbiotic-like relationship between two partners, we can genetically engineer the donor cell to become mutual interdependence on recipient cell for survival. Two complementary strategies have proven effective to boost the likelihood of endosymbiogenesis (Figure 1C). One is rational design combined with genetic manipulation, exemplified by the construction of a photosynthetic yeast-cyanobacterium chimera, where cyanobacteria were engineered for carbon assimilation and sugar secretion to support yeast hosts.[7] The other is adaptive evolution, including approaches such as repeatedly isolating bacteria-harboring fungal spores via flow cytometry to stabilize symbiosis,[8] or engineering hypermutable bacterial strains—by disrupting DNA repair genes—to accelerate adaptation through elevated mutation rates.[9]

Once a model of endosymbiosis is established, we will have the possibility to understand the principles governing the establishment and the maintenance of an endosymbiotic-like association, and how such a relationship can confer new traits upon host cells. With the powerful gene editing technology

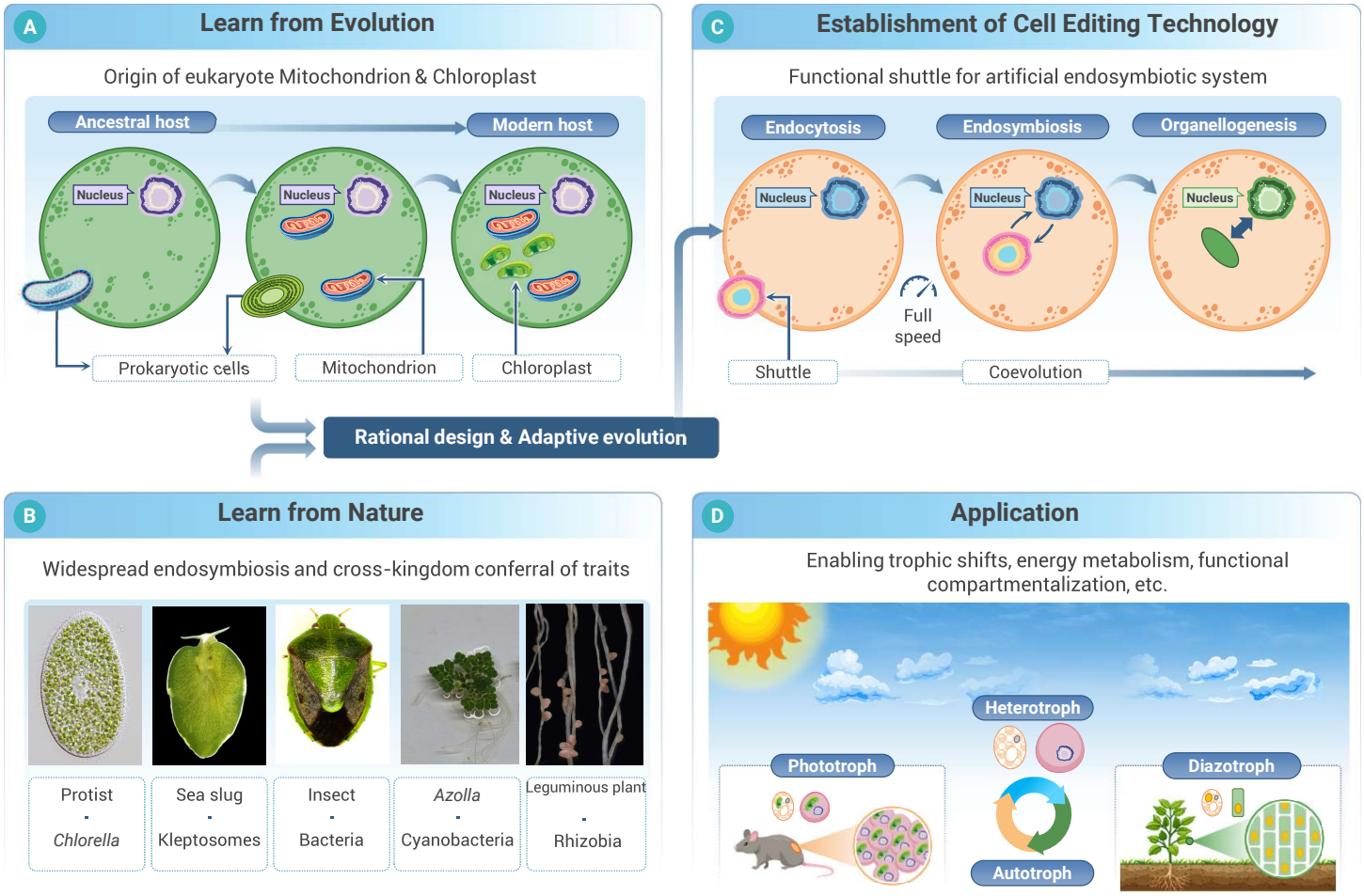

Figure 1. Development of cell editing technology (A) The endosymbiotic theory holds that mitochondria and chloroplasts originate from mutualistic symbiotic relationships formed after ancestral host engulfed prokaryotic cells, eventually evolving into organelles. (B) Endosymbiosis events are prevalent in nature and can confer functional traits across species. Examples include protist and *chlorella*, sea slug and kleptosomes, insect and bacteria, *Azolla*-cyanobacteria, as well as leguminous plant and rhizobia. (C) Knowledge about the evolutionary history of endosymbiosis and its widespread manifestations in nature can be the driving force for the establishment of artificial cell editing technology. Rational design and adaptive evolution could be applied to the construction of endosymbiotic shuttles by multiple rounds of engineering, accelerating the process of endosymbiosis establishment to a timescale feasible in laboratory settings. (D) The establishment of this new technology will open up immense application scenarios, enabling biological trophic shifts, reconstruction of energy metabolism, formation of organelle-based functional compartments, etc. Image sources (left to right): protist and *Chlorella* (J. Xiong, Institute of Hydrobiology, CAS), sea slug and kleptosomes (X. Wang, South China Sea Institute of Oceanology, CAS), insect and bacteria (adapted from Koga R, et al. 2022,[9] CC BY 4.0; https://creativecommons.org/licenses/by/4.0), *Azolla*-cyanobacteria (J. Zhan, Institute of Hydrobiology, CAS), and leguminous plant and rhizobia (X. Zhang, Center for Excellence in Molecular Plant Sciences, CAS).

now available, it may enable the engineering of microbial cells finally as the "functional shuttle" carrying a special function, conferring a wide range of hosts a novel and complex traits that is difficult to achieve with current technology. Here, we defined functional shuttle as an engineered cell or organelle designed to establish a mutually interdependent relationship with host via anti-rejection, synchronized division, and metabolic complementation to stably deliver complex traits to host.

Drawing on recent advances, the formation of endosymbiosis appears to involve convergent evolution across species, with mechanistic links to cellular phagocytic processes and potentially autophagy-like or endosome in plants.[4,10] Modulating the phagosome and its fusion with lysosomes or vacuole to achieve a balance between degradation and persistence may represent a universal strategy for engineering artificial endosymbiosis. Rational design of digestion-resistant shuttles, reprogramming of host digestive pathways, as well as mitigation of immune rejection and facilitation of metabolic complementarity, will be key considerations in future efforts to build stable artificial endosymbiotic systems.

The potential applications of this technology are profound. It could enable fundamental biological alterations, including trophic shifts, metabolic reconstruction, and cellular compartmentalization. Among the most ambitious envisioned applications are engineering nitrogen fixation into non-symbiotic plants and conferring autotrophic or even photosynthetic capabilities to complex animals, with such advancements remaining, for now, largely speculative (Figure 1D). The successful development of such systems relies on the ability to overcome natural evolutionary barriers, enabling new endosymbiotic-like partnerships easily established between bacterial or eukaryotic cells and eukaryotic systems, including protists, plants and animals. Due to the complexity of developing such systems, collaborative efforts involving scientists from various backgrounds, including microbiology, plant and animal science, genomics, bioinformatics, cell biology, genetics, artificial intelligence etc., would be the key to the success of such an endeavor. The recently launched project by the Chinese Academy of Sciences (CAS) will push a collaborative effort to develop these research frontiers, an opportunity for the research community to advance our understanding of not only the principles underlying symbiosis, but also to develop potential technology arising from such studies.

The construction of chimeric organisms will raise biosafety and ethical concerns. Technical safeguards such as endosymbiosis termination elements should be introduced to prevent uncontrolled release. Ethically, regulatory frameworks are needed to ensure legal oversight, monitoring, and science communication.

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AUTHOR CONTRIBUTIONS

C. Zhang, W. Miao and K. Huang, are the originators of the core conceptual framework. Y. Deng and J. Xiong are responsible for the comprehensive collection and critical synthesis of relevant literatures, and the figure. All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.

ETHICAL STATEMENT AND PATIENT CONSENT

Not Applicable.