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Design, analysis and application of synthetic microbial consortia

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ABSTRACT

The rapid development of synthetic biology has conferred almost perfect modification on single cells, and provided methodological support for synthesizing microbial consortia, which have a much wider application potential than synthetic single cells. Co-cultivating multiple cell populations with rational strategies based on interacting relationships within natural microbial consortia provides theoretical as well as experimental support for the successful obtaining of synthetic microbial consortia, promoting it into extensive research on both industrial applications in plenty of areas and also better understanding of natural microbial consortia. According to their composition complexity, synthetic microbial consortia are summarized in three aspects in this review and are discussed in principles of design and construction, insights and methods for analysis, and applications in energy, healthcare, etc.

1. Introduction

With the rapid development of synthetic biology, designing and constructing synthetic microbial consortia has raised extensive attention, becoming one of the important frontiers for the second wave of synthetic biology,[1] but yet to be an important aspect of in-depth research.[2] As summarized by Ron Weiss and Cynthia Collins, there are three advantages of taking microbial consortia as the research object to engineer specific routes: (1) different strains are functionally divided to fulfill many complex tasks at the same time; (2) relationships between cells are dynamically balanced, leading to stronger adaptability and stability to the fluctuant environment; (3) elements and modules from different sources and with different functions can be built in different strains, reducing the metabolic load on single chassis as well as avoiding the cross-influence of different functions.[3,4]

There are mainly two ways for designing and constructing synthetic microbial consortia. The first one is to re-engineer naturally occurring microbial consortia, which is a top-down method.[5] That is, based on multiple omics analysis,[6–12] starting from the macroscopic microbial consortia, parsing the system principles, to explore the molecular mechanisms for the maintained systems. The other one is to design and construct artificial microbial consortia, which is a bottom-up method.[5] That is, based on the genetic elements, modules, circuits and metabolic pathways or networks,[13–16] with the rational guidance of engineering principles, to obtain microbial consortia with higher efficiency, stability and controllability. Considering the complexity and practicability of synthetic biology, currently the bottom-up method is the mostly used for constructing microbial consortia from simple to complicated. Moreover, about the synthetic systems, there are different statements on the concept: co-cultures,[17,18] mixed cultures,[19] microbial consortia,[4,20] and so on. Considering that the phrase “microbial consortia” indicates not only living together but also labor division, and covers all of conditions of their composition: by single, two, and multiple species,[2,6,21] we use “microbial consortia” in this review.

This review summarized current synthetic microbial consortia reported in literature from three aspects according to their composition complexity (composed of single species, two species or multiple species) and then discussed their design and construction strategies based on the interactions within microbial communities, their mechanism analysis methods, as well as their applications in many fields such as medicine and energy, etc.

2. Synthetic microbial consortia composed of single species

Research on synthetic microbial consortia composed of single species mainly focuses on pattern microbes, such as *Escherichia coli* and *Saccharomyces cerevisiae*, which have clear genetic backgrounds and mature molecular technologies. It mainly focuses on cell–cell communications and interaction analysis within the ecosystems.

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2.1. Design and construction of synthetic microbial consortia composed of single species

One of the basic cell–cell communications for constructing synthetic microbial consortia is quorum sensing (QS). The key of QS is some signaling molecules known as autoinducers, which diffuse from intracellular to extracellular. When reaching a certain threshold (usually in high cell concentration), they trigger or coordinate the expression of certain genes. Except communications within populations, one-way interactions between populations such as a pulse-generator system,[22] a pattern formation programming system,[23] and a sender–receiver communication network[24] are equally employed. Besides, there are two-way interactions. Brenner et al.[21] constructed a consortium with LasR/LasI and RhlR/RhlI QS systems in which gene-expression response if and only if both populations are present over a threshold cell densities (Fig. A1). These are all the basic interaction modes between microorganisms, revealing the molecular mechanisms, which provide the basis for the design of synthetic microbial consortia.

The most well studied form of QS is spatio-temporal, by which population density is coupled with some special module, with the help of a fluorescent protein, the consortia is periodically distributed.[25–29] For example,[30] the coupling of LasR/LasI as a density-sensing module, and coupling it with motility-control modules in *E. coli* could command population behavior: high cell density stopped the motility while low cell density drove the movement, according to the density difference, light and dark circular pattern were gradually formed (Fig. A2).

Recently, QS has been developed with more complicated population behavior and more novel control. Using the LasR/LasI and two dispersal proteins, a colonizer–disperser consortium is designed to control the biofilm breakdown, movement and formation.[31] Combining the LuxR/LuxI with a CcdA/CcdB toxin–antitoxin module, a typical Allee effect was constructed, which caused a tradeoff between population spread and survival.[32] Payne et al.[33] broke the traditional spatial cue for pattern formation which depended on morphogen gradient, using the morphogen served as a timing cue to trigger the formation and maintenance of the ring patterns.

Of course, QS is not the only principle for designing the communities. Based on nutrition complementarity, microbes can form symbiosis relationship, such as consortium composed of isoleucine auxotroph and leucine auxotroph, strains not only acquired what they lacked, but also over-supplied amino acids required for partner

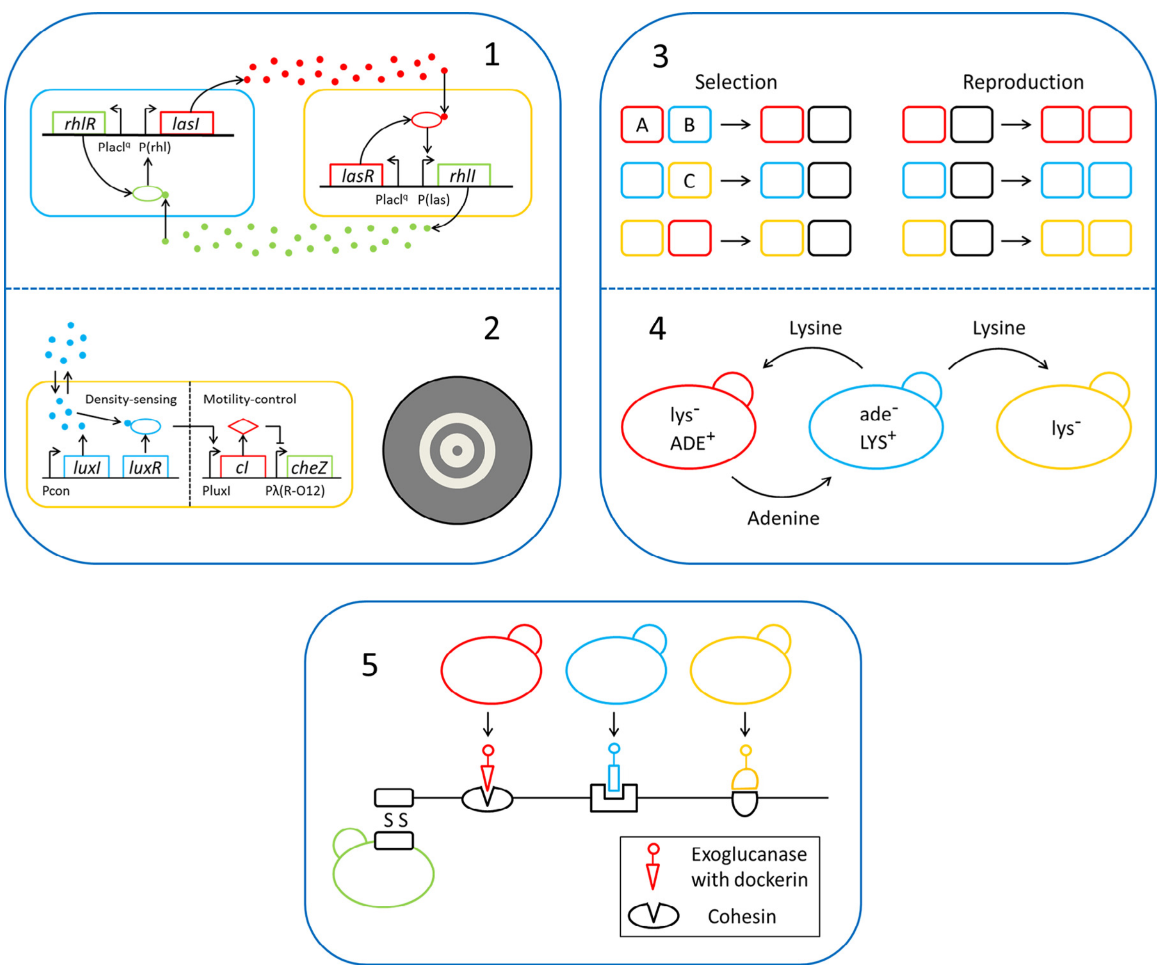

Fig. A. Design, analysis and application of synthetic microbial consortia composed of single species. (1) A bidirectional QS system. (2) A spatio-temporal system coupled QS and density-sensing module. (3) Local reactions of designed rock–paper–scissors relationship. (4) Interactions of a cooperator–cheater system. (5) A minicellulosome yeast consortium. Part 1 is adapted by permission from *Proceedings of the National Academy of Sciences*[21] ©. Part 2 is adapted by permission from *Science*[30] ©. Part 3 is adapted by permission from Macmillan Publishers Ltd: *Nature*[43] ©. Part 4 is adapted by permission from *Proceedings of the National Academy of Sciences*[45] ©. Part 5 is adapted by permission from *Microbial Cell Factories*[49] ©.