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Design and construction of synthetic microbial consortia in China

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ABSTRACT

The rapid development of synthetic biology enables the design, construction and optimization of synthetic microbial consortia to achieve specific functions. In China, the "973" project-"Design and Construction of Microbial Consortia" was funded by the National Basic Research Program of China in January 2014. It was proposed to address the fundamental challenges in engineering natural microbial consortia and reconstructing microbial consortia to meet industrial demands. In this review, we will introduce this "973" project, including the significance of microbial consortia, the fundamental scientific issues, the recent research progresses, and some case studies about synthetic microbial consortia in the past two and a half years.

Contents

1. Introduction

In natural environments, 99% microorganisms exist in the form of microbial consortia. However, some defects of naturally occurring microbial consortia, such as difficulty in culturing, long operation cycle, low conversion efficiency, and poor stability and controllability, limited their practical applications in biotechnology industries. Synthetic microbial consortia constructed via synthetic biology approaches would be an alternative for programming novel complex behaviors and optimal features for practical biotechnology applications. Arnold [1] and Weiss [2,3] pointed out that synthetic microbial consortia could perform even more complicated tasks and endure more changeable environments than that of monocultures, thus providing an important new frontier for synthetic biology. A better knowledge of the multicellular systems that drive cell-cell interactions in the consortia was highly needed [4,5]. Engineering novel cell-cell interaction capabilities became crucial in the nascent field of synthetic biology [2].

Recently, scientists have made great progresses about analysis,

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design and construction of microbial consortia (Fig. 1). Stephanopoulos et al. constructed an *Escherichia coli- Saccharomyces cerevisiae* consortium to successfully produce oxygenated taxanes [6], and an *E. coli- E. coli* consortium to produce muconic acid [7,8] and 3-amino-benzoic acid [9]. Jones and his colleges [10] constructed an *E. coli- E. coli* co-culture for the efficient production of flavonoids. Lin et al. [11] designed and constructed a fungal-bacterial consortium to efficiently produce isobutanol from cellulose. Shou et al. [12–14] have been focused on engineering and analyzing the underlying mechanisms of cell-cell communication for many years. A series of synthetic syntrophic communities were constructed to probe the metabolic cross feeding principles underlying the complex microbial consortia [15–19].

In the USA, Defense Advanced Research Projects Agency (DARPA) announced a funding entitled “Biological Robustness in Complex Settings (BRICS)” in August 2014. The BRICS program aimed to design synthetic communities consisting of multiple organisms and to elucidate the design principles of engineering robust microbial consortia. The end-program objective is to engineer robust, stable, and safe bio-systems. In China, the “973” project-“Design and Construction of Microbial Consortia”, funded by the National Basic Research Program of China in January 2014 was proposed to address fundamental challenges in engineering natural microbial consortia and reconstructing artificial microbial consortia to meet industrial demands. Great progresses were made in China about the analysis, design, construction of microbial consortia related to microbial fuel cells (MFCs) [20], vitamin C fermentation [21,22], polyhydroxyalkanoate (PHA) production [23], methane production [24], wastewater treatment [25], biodegradation [26], etc. For further design and construction of synthetic microbial consortia, a synthetic biology module library SynbioML@TJU (http://www.synbioml.org/) that contains more than 5000 artificial synthetic genes and functional modules for diverse products was established by Tianjin University, China. SynbioML covers synthetic genes and functional modules for biosynthesis of natural products (terpenes, flavonoid, polyketones, alkaloids, etc), chemical products (steroids, aminoglycosides, polypeptides, etc), nutrition and health care products (fatty acids, vitamins, etc), biofuels (bioethanol, aliphatic alcohols, butanediol, etc), environmental biological sensors, microbial fuel cells, etc. All of the physical modules, preserved at Tianjin University, can be freely obtained through SynbioML website. Users can search for modules in the website by gene name, protein name, E.C. number, metabolic pathway, enzyme reaction etc.

2. “973” project about microbial consortia in China

To obtain high-efficient, stable, and controllable synthetic microbial consortia, two predominant, fundamental scientific issues were needed to be addressed in this “973” project (Fig. 2): (1) the principles in the design and construction of microbial consortia to make microbes work together; (2) the fitness and regulation mechanisms in synthetic microbial consortia to make microbes work better.

The design principles for synthesizing microbial consortia mainly based on the interaction modes among microbes, including cell-cell communications, and exchange of metabolites and energy, etc. In the natural microbial consortia, there are many ways of interactions according to the modes of metabolic exchange, including commensalism, synergism, mutualism, competition, neutralism, parasitism, and predation, etc. The stable interaction generally relied on the intercellular communication among cells by means of co-utilization of different substrates in the environment, sequential conversion of substrates and reutilization, complement of metabolite, and other ways to meet normal growth of individual cells in multicellular systems. Understanding the cooperative mechanisms in naturally occurring communities would be helpful for designing synthetic microbial consortia. Systems biology could offer insights into the rational design and construction of microbial consortia, and provide detailed molecular understanding of the synthesized microbial ecosystems by rational design strategies [27].

In the synthetic microbial consortia, the partition of different functional modules is benefit for the achievement of orthogonality among modules. However, the partition that achieved by cell membrane would affect the recognition of signal molecule, and

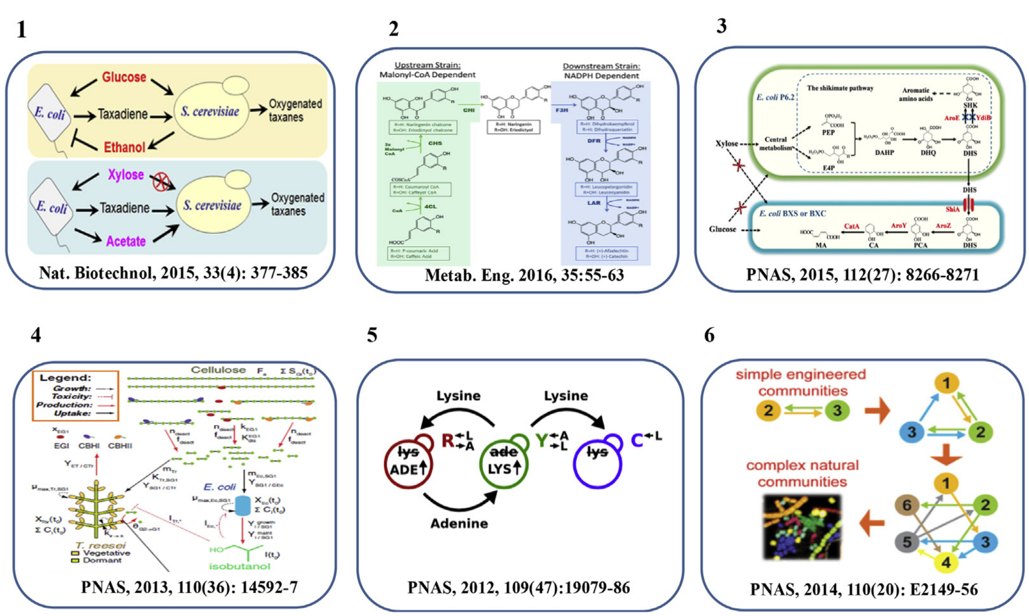

Fig. 1. Applications of synthetic microbial consortia. Part 1 is adapted by permission from Nature Biotechnology [6] ©. Part 2 is adapted by permission from Metabolic Engineering [10] ©. Part 3 is adapted by permission from Proc Natl Acad Sci USA [7] ©. Part 4 is adapted by permission from Proc Natl Acad Sci USA [11] ©. Part 5 is adapted by permission from Proc Natl Acad Sci USA [12] ©. Part 6 is adapted by permission from Proc Natl Acad Sci USA [15] ©.