Biotechnology Advances 33 (2015) 1412–1419

Contents lists available at ScienceDirect

Biotechnology Advances

journal homepage: www.elsevier.com/locate/biotechadv

Research review paper

Modularization of genetic elements promotes synthetic metabolic engineering

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ARTICLE INFO

Available online 11 April 2015

Keywords:
Synthetic biology
Modularity engineering
Modularization
DNA assembly

ABSTRACT

In the context of emerging synthetic biology, metabolic engineering is moving to the next stage powered by new technologies. Systematical modularization of genetic elements makes it more convenient to engineer biological systems for chemical production or other desired purposes. In the past few years, progresses were made in engineering metabolic pathway using synthetic biology tools. Here, we spotlighted the topic of implementation of modularized genetic elements in metabolic engineering. First, we overviewed the principle developed for modularizing genetic elements and then discussed how the genetic modules advanced metabolic engineering studies. Next, we picked up some milestones of engineered metabolic pathway achieved in the past few years. Last, we discussed the rapid raised synthetic biology field of "building a genome" and the potential in metabolic engineering.

Contents

1. Introduction

Regulation system within cell is extremely complicated than as expected. Although efforts have been paid continually for decades in metabolic engineering, harnessing cells as bio-factory for synthesis of natural compounds or chemicals still remains a huge challenge. However, metabolic engineering holds great potential in addressing issues in environmental pollution and exhaustion of limited natural resource. Recently, new technologies emerging from synthetic biology pave the way for metabolic engineering cells to meet our increasing application requirements. The core of synthetic biology comes down to the application of basic principles of engineering to the fundamental biological systems (Andrianantoandro et al., 2006; Church, 2005; Endy, 2005; Khalil and Collins, 2010; Liang et al., 2011; McDaniel and Weiss, 2005; O'Malley et al., 2008; Purnick and Weiss, 2009; Zhang et al., 2011). With learning lots from the traditional mechanical and electrical engineering, standardization of genetic elements in biological system is able to maximize the compatibility, interoperability, repeatability and quality in customized applications with specific goal. Especially, these new paradigms of organizing genetic components into exchangeable modules match the requirement of metabolic engineering applications. Obviously, modularization of genetic elements will make it more convenient to improve the performance of engineered cells with heterologous metabolic network. In addition, modularized genetic elements could advance the applications of creating artificial metabolic pathway. Herein, we review the recent progresses in the modularization of

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http://dx.doi.org/10.1016/j.biotechadv.2015.04.002
0734-9750/

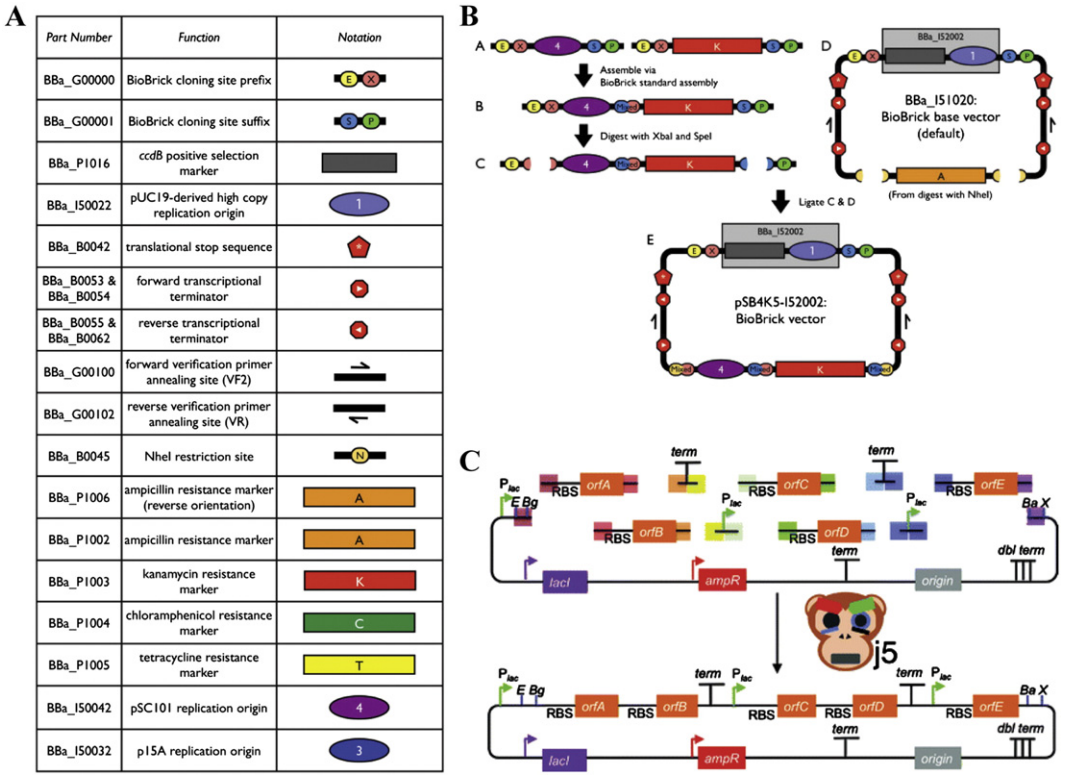

Fig. 1. Modularization of genetic elements. A. Example of functional DNA parts registered in BioBrick registry (adopted from ref. (Shetty et al., 2008)). B. DNA modules of BioBricks assembly processes (adopted from ref. (Shetty et al., 2008)). C. The schematic for J5 DNA assembly design automation software (adopted from ref. (Hillson et al., 2012)).

genetic elements for metabolic engineering to purchase the goal of biosynthesis of value-added chemicals in systematic way.

2. Modularization of genetic elements

Standardization of the genetic elements is the base for modularization. The core concept of BioBrick first proposed the standardization of the DNA tails and the endonuclease sites, which succeeded to promote the studies on modularization of genetic elements (Canton et al., 2008; Constante et al., 2011; Shetty et al., 2008; Smolke, 2009). The genetic components such as promoter, terminator, coding sequence, and ribosome binding site were defined as exchangeable lego-like DNA part (Shetty et al., 2008) (Fig. 1A). Therefore, various features for regulation of gene expression could be created easily with simple combination of the related BioBrick DNA parts (Fig. 1B). Thus far, there are over 5000 parts in the database of Standard Biological Parts registry (Norville et al., 2010). As being a creative platform, BioBrick has inspired development of many related technologies, such as BglBrick (Anderson et al., 2010) and optimized DNA assembly methods (Hatfield and Roth, 2007; Ho-Shing et al., 2012; Shetty et al., 2011; Sleight et al., 2010). Another potential advantage of standardization is the ease for automation. Computer assistant DNA assembly software has been developed (Table 1) (Chen et al., 2012; Hatfield and Roth, 2007; Hillson, 2014; Leguia et al., 2011; Rodrigo et al., 2012; Wright et al., 2014; Wu and Rao, 2012). For example, the J5 DNA assembly design automation software was proven as a powerful tool for scar-less DNA assembly based on various assembly principles (Fig. 1C) (Hillson et al., 2012). Genome editing suite BioStudio was proven as a powerful tool for in silico genome design (Dymond et al., 2011). R2oDNA designer, a website based application, enables people to design neutral DNA sequences (Casini et al., 2014). However, due to the lack of knowledge about the whole picture of gene expression regulation, there is still no universal standard for designing genetic module in mammalian cells. On the other hand, technically most of the mammalian genetic elements could be incorporated into the well-developed model cells, e.g. *Escherichia coli* and yeast, based on the current modularization standards.

Table 1
Selected computational program for construction of synthetic DNA module.

Design program	Web URL	Feature	References
J5	http://j5.jbei.org	Designing multipart DNA assembly based on sequence-independent overlap protocols including the SLIC, Gibson and CPEC.	(Hillson, 2014; Hillson et al., 2012)
AtuoBioCAD	http://jaramillolab.issb.genopole.fr/display/sbsite/Download	Designing DNA sequence for construction of genetic circuit module of logic control function.	(Rodrigo and Jaramillo, 2013)
SBROME	http://tagkopouloslab.ucdavis.edu/software.html	Designing DNA sequence for construction of genetic circuit module of logic control function	(Huynh et al., 2013)
D-Tailor	http://sourceforge.net/projects/dtailor	Designing DNA sequence with desired function for gene expression.	(Guimaraes et al., 2014)
Eugene	http://eugene.sourceforge.net	Integrated domain specific program for construction of genetic system from set of standardized DNA parts.	(Bilitchenko et al., 2011)
Gene Designer 2.0	http://www.dna20.com/resources/genedesigner	Fast and easy design of gene from basic function elements using advanced optimization algorithms.	(Villalobos et al., 2006)
GenoCAD	http://genocard.org	Customisable rube-driven design of genetic sequences	(Wilson et al., 2011)
R2oDNA	http://www.r2odna/com	Program for stochastically creating orthogonal DNA sequence.	(Casini et al., 2014)