# Metabolic engineering: Tools and applications



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Editorial

# Metabolic engineering: Tools and applications

Metabolic engineering plays a pivotal role in the development of microbial cell factories for efficient production of biofuels, chemicals, and natural products, which facilitate the transition from fossil-resource dependent processes to green and sustainable bio-based processes. By doing so, we could address global challenges such as sustainability, human health, and climate change. Significant progresses in economical chemical bioproduction have been accomplished by improving the physiological properties of microbial cells through metabolic engineering [1]. However, to encourage a shift towards circular bio-economies, the performance of microbial cell factories must become more cost-effective. Therefore, there is a strong demand for innovative techniques that, upon application, can greatly speed up the classic design-build-test-learn (DBTL) cycle in metabolic engineering.

This special issue was aimed to showcase some recent advances in developing novel synthetic biology tools and screening techniques for metabolic engineering, strategies on engineering of microbial cell factories for sustainable feedstock utilization, and the production of representative chemicals.

## 1. Advances in metabolic engineering tools

The development of genetic engineering tools, gene regulation methods, and high throughput screening techniques are crucial for speeding up cell factory construction. In this special issue, Wu et al. reviewed recent advances in genetic tools for a methylotrophic yeast *Pichia pastoris* [2]. These advances will facilitate the engineering of this yeast for heterologous protein production and utilizing one carbon compound methanol for chemical synthesis. Dynamic regulation of gene expression allows organisms to adapt their metabolic states to the changing intracellular or environmental conditions in real time. Xiao et al. demonstrated dynamic regulation as an effective strategy for optimizing metabolic fluxes and improving production efficiency [3].

In addition, high throughput screening plays a vital role in improving the physiological properties of cell factories. To generate genetic diversity, pooled CRISPR technology has becoming a powerful approach. Sun et al. provides an overview of the recent progress made in pooled and arrayed CRISPR interference screening in microorganisms [4]. In this context, Mukherjee et al. [5] employed CRISPR interference screening to identify chromatin regulation mechanisms associated with formic acid tolerance in *Saccharomyces cerevisiae*. While screening for phenotypes related to cell growth or strain tolerance is relatively straightforward, it is ideal to develop biosensors capable of sensing the metabolite concentrations and converting them to fluorescence signals for the screening of strains with improved chemicals synthesis capabilities. Chao et al. [6] developed a highly selective fluorescent biosensor for genistein detection, facilitating the screening of genistein high producers. This design principle holds great potential for the construction of biosensors for various other chemicals.

## 2. Utilization of renewable resources

The bioconversion of highly abundant renewable resources, including one carbon (C1) compounds and lignocellulose biomass, not only provides alternative routes to produce fuels and chemicals, but also contributes to climate change mitigation. Methanol, derived from methane, carbon dioxide, or other industrial waste gases, is an important C1 compound. Gan et al. [7] summarized both natural and synthetic methanol assimilation pathways and reviewed metabolic engineering strategies for microbial methanol utilization. Qiu et al. [8] provided an overview on metabolic engineering strategies for xylose utilization, a key component of lignocellulosic biomass. These advances offer the guidance for achieving a low-carbon footprint for chemical biosynthesis.

## 3. Microbial cell factories for chemical production and protein expression

The production of chemicals biologically from renewable resources offers a sustainable alternative to petrochemical-based chemical production. It is estimated that the production of biobased chemicals can yield an annual revenue of US$10–15 billion in global chemical industry [9]. Amino acids and vitamins are important nutrients for human and animals. Microbial fermentation contributes to 80 % of global amino acid production, while the production of many vitamins still relies on chemical synthesis. Tuo et al. [10] reviewed recent advances in screening amino acids overproducers. Gu et al. [11] engineered *Saccharomyces cerevisiae* for improved production of 7-dehydrocholesterol, a key intermediate for vitamin D3 synthesis. Related studies will promote the biosynthesis of vitamins. In addition to amino acids and vitamins, many natural products, such as terpenes, have also been produced using microbial cell factories. Lu et al. [12,13] engineered yeast for terpene production and identified the role of Hxk2 degradation in regulating glucose depression and improving terpene synthesis through proteomics analysis. This highlights the importance of metabolic network regulation in improving chemicals synthesis.

Microbial cell factories are not limited to chemical production. They can also produce recombinant enzymes/proteins for industrial or clinical applications. Yang et al. [14] offered an extensive review on recent advances in engineering microorganisms for protein secretion, providing valuable guidance for improving recombinant protein expression. As a practical demonstration, Liao et al. [15] expressed a Leech

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hyaluronidase on the yeast cell surface to catalyze the conversion of high molecular weight hyaluronic acid to low molecular weight hyaluronic acid, a popular ingredient in clinical treatments and cosmetic care.

In summary, with the development of synthetic biology tools, metabolic engineering will continuously contribute to replacing petroleum derived products with biologically produced renewable alternatives, making the world a better place for both humans and the environment.

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Yun Chen
*Department of Biology and Biological Engineering, Chalmers University of Technology, Gothenburg, Sweden*

Jiazhang Lian
*Key Laboratory of Biomass Chemical Engineering of Ministry of Education, College of Chemical and Biological Engineering, Zhejiang University, Hangzhou, China*

Jin Hou*
*State Key Laboratory of Microbial Technology, Shandong University, Qingdao, China*

*Corresponding author.
*E-mail address:* houjin@sdu.edu.cn (J. Hou)