Class I Polyhydroxyalkanoate (PHA) Synthase Increased Polylactic Acid Production in Engineered Escherichia Coli

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Polylactic acid (PLA), a homopolymer of lactic acid (LA), is a bio-derived, biocompatible, and biodegradable polyester. The evolved class II PHA synthase (PhaC1Ps6-19) was commonly utilized in the de novo biosynthesis of PLA from biomass. This study tested alternative class I PHA synthase (PhaCs) from Chromobacterium sp. USM2 in engineered Escherichia coli for the de novo biosynthesis of PLA from glucose. The results indicated that PhaCs had better performance in PLA production than that of class II synthase PhaC1Ps6-19. In addition, the sulA gene was engineered in PLA-producing strains for morphological engineering. The morphologically engineered strains present increased PLA production. This study also tested fused propionyl-CoA transferase and lactate dehydrogenase A (fused PctCp/LdhA) in engineered E. coli and found that fused PctCp/LdhA did not apparently improve the PLA production. After systematic engineering, the highest PLA production was achieved by E. coli MS6 (with PhaCs and sulA), which could produce up to 955.0 mg/L of PLA in fed-batch fermentation with the cell dry weights of 2.23%, and the average molecular weight of produced PLA could reach 21,000 Da.

Keywords: class I polyhydroxyalkanoate synthase, engineered E. coli, polylactic acid, biopolyester, degradable polymer

INTRODUCTION

Biopolymesters have been developed in recent years as alternatives to petroleum-based synthetic polyesters (Nduko and Taguchi, 2021). As a commercialized biopolyester, polylactic acid (PLA) can be prepared from renewable biomass with promising physical performance, biocompatibility, and biodegradability (Taguchi et al., 2008; Yang et al., 2010; Paço et al., 2019). The industrial preparation of PLA is accomplished through several steps: first, the monomer of lactic acid (LA) is prepared from biomass through fermentation; then LA is converted to lactide followed by the ring-opening polymerization of lactide to PLA (Maharana et al., 2009).

With the fast development of biotechnology, PLA homopolymer and LA-containing copolymers can be de novo biosynthesized from renewable biomass by engineered strains (Taguchi et al., 2008; Yang et al., 2010; Choi et al., 2016; Zou et al., 2021). However, compared with the efficient bioproduction of LA-containing copolymers, the microbial production of PLA homopolymers is still
challenging with low productivity. One of the barriers in the biosynthesis of the PLA homopolymer is that the PHA synthases involved exhibit higher activities toward other substrates than LA monomer (Park et al., 2012).

Based on the primary structure, subunit compositions, and substrate specificity, four classes of PHA synthases have been found in nature (Yang et al., 2010; Zou et al., 2017; Chek et al., 2019). Class I, III, and IV PHA synthases prefer short-chain length (SCL) monomers, whereas class II PHA synthases exhibit higher activities toward medium-chain length (MCL) monomers (Rehm, 2003; Tsuge et al., 2015; Zou et al., 2017). Class II synthase can affect the formation of the Z ring during bacteria division and hence enlarge cell space (Dajkovic et al., 2008; Adams and Errington, 2009; Chen et al., 2012). Higher expression of SulA can inhibit FtsZ and reduce the cell division rate (Dajkovic et al., 2008; Chen et al., 2012). For example, morphologically engineered E. coli JM109 exhibits the increased production of poly (3-hydroxybutyrate) (PHB) (from 8 to 9 g/L) and poly (3HB-co-4HB) (from 8.2 to 9.2 g/L) (Wang et al., 2014; Wu et al., 2016).

In this study, to screen robust PHA synthase in PLA biosynthesis, we selected the class I PHA synthase from Chromobacterium sp. USM2, which has been used in the polymerization of 3-hydroxypropionic acid (3HP, an isomer of LA) (Linares-Pastén et al., 2015), and evaluated its performance in PLA homopolymer production by engineered E. coli. In addition, we additionally expressed the sulA gene and evaluated the PLA production of morphologically engineered strains.

### MATERIALS AND METHODS

#### Strains and Engineering Methods

All the information on strains and plasmids is listed in Table 1. The information of key plasmids is provided in Supplemental Table S1. The primers are summarized in Supplemental Table S1. Engineered strains were constructed using the following methods.

The suicide plasmid–mediated genome editing method (Gao et al., 2014) was utilized in the deletion of the ackA gene from the genome of E. coli BL21 (DE3). The homolog arms (600 bp upstream and downstream of the ackA gene) were cloned into...
the suicide plasmid of pRE112. The constructed pRE112-ΔackA was transformed into E. coli χ7213 to construct the donor strain of E. coli χ7213/pRE112-ΔackA. Then, the conjugation occurred between the donor strain and the receptor strain of E. coli BL21 (DE3) for the deletion of the ackA gene. The strain of E. coli MS1 (Table 1) was constructed after knocking off ackA.

Based on the chassis strain of E. coli MS1, other engineered strains (MS2–MS7) were constructed using the following methods. As shown in Figure 1, the biosynthetic pathway of PLA was engineered in PLA-producing strains; in addition, the sulA gene was expressed in strains for larger cell space.

From E. coli MS1, E. coli MS2 additionally expressed the ldhA gene from E. coli BL21 (lactate dehydrogenase, NCBI No. NC_012892.2). From E. coli MS2, E. coli MS3 additionally expressed the evolved PctCp gene (propionyl-CoA transferase, NCBI No. CAB77207.1, with mutation of V193A) from Clostridium propionicum DSM 1682 and the evolved PhaC1Pb-19 gene (class II PHA synthase, NCBI No. ACM68707.1, with mutations of E130D, S325T, S477G, and Q481K) from Pseudomonas sp. MBEL 6-19. From E. coli MS3, E. coli MS4 additionally expressed the sulA gene from E. coli str. K-12 substr. MG1655 (NCBI No. NC_000913.3).

From E. coli MS2, E. coli MS5 additionally expressed the evolved PctCp gene from C. propionicum and the PhaC1Cp gene (class I PHA synthase, NCBI No. ADL70203.1) from Chromobacterium sp. USM2. From E. coli MS5, E. coli MS6 additionally expressed the sulA gene from E. coli str. K-12. From E. coli MS1, E. coli MS7 additionally expressed the gene of the fused enzyme of PctCp/LdhA (Supplemental Figure S2). A flexible linker (Gly−Gly−Gly−Gly−Ser)_3 was inserted between PctCp and LdhA; in addition, E. coli MS7 expressed the evolved PhaC1Pb-19 gene from C. propionicum and the sulA gene from E. coli str. K-12.

**Flask and Fed-Batch Fermentation**

All strains utilized in this study are cultivated in the Luria–Bertani (LB) medium (flask-level) or M9 medium (fermenter-level). The LB medium contains (per liter) 10 g tryptone, 5 g yeast extract, and 10 g NaCl. The M9 medium consists of (per liter) 1 g (NH₄)₂SO₄, 3 g K₂HPO₄, 3H₂O, 1.9 g KCl, 5 g yeast extract, 1 g sodium citrate, 1 g citric acid, 1 g glucose, 0.24 mg MgSO₄, and 1 ml of the stored solution of trace element. The stored solution of trace element consists of (per liter) 3.7 g (NH₄)₆Mo₇O₂₄·4H₂O, 2.9 g ZnSO₄ 7H₂O, 24.7 g H₂BO₃, 2.5 g CuSO₄ 5H₂O, and 15.8 g MnCl₂ 4H₂O. Variable antibiotics were supplemented in the cultivation medium for different strains (Table 1). The concentration of antibiotics in the medium is as follows: ampicillin 48 mg/L, chloramphenicol 24 mg/L, and kanamycin 45 mg/L. The sucrose-containing (10% w/w) LB medium was utilized to screen the strain of E. coli MS1.

For fermentation of PLA, individual strains were cultivated in 10 ml LB medium at 37°C overnight in a rotary shaker at 220 rpm. Then, 5% (V/V) seed cultures were added into 100 ml LB medium (in a flask) and cultivated at 37°C overnight in a rotary shaker at 220 rpm. The secondary seed cultures were inoculated into a 5-L fermentor (Bailun Inc., China) containing 2 L M9 medium, and 20 g/L glucose was added as a starting carbon source. Fed-batch fermentation starts at 37°C. During the fermentation process, ammonium hydroxide solution (6M) was automatically added to maintain the pH at 7. The dissolved oxygen concentration (DOC) was maintained at 10–20% by changing the agitation speed and ventilatory capacity (VC). Ten hours after inoculation, 0.5 mM of...
isopropyl-β-D-thiogalactopyranoside (IPTG) was added in the fermenter, and then the cultivation temperature was decreased to 30°C. Then, 100 ml of 50% glucose (w/v) was supplemented every 12 h. The cell growth value of OD600 was monitored using the spectrophotometer at 600 nm. The duration time of fermentation was 72 h.

**Analytical Methods**

The solvent extraction method (Jung et al., 2010) was utilized for the purification of PLA products from the cells. After fermentation, the cells were harvested by centrifugation at 4000 rpm for 20 min. The harvested cells were washed twice with absolute ethanol and distilled water before lyophilization. Then, the cells were lyophilized for 24 h and the cell dry weights (CDW) of different samples were measured and recorded. PLA was extracted from dried cells by chloroform in the Soxhlet apparatus at 80°C for 16 h. Excessive chloroform was removed and dried cells by chloroform in the Soxhlet apparatus at 80°C for 16 h. Excessive chloroform was removed and cell debris was removed by passing through a PTFE filter. PLA was precipitated by adding five-fold ice-cold methanol. Weights of purified and dried PLA was measured and recorded.

To qualitatively determine the polymer structure, the samples were analyzed by 1H and 13C nuclear magnetic resonance (NMR) spectra using a Bruker AM-500 MHz spectrometer at 500 and 125 MHz, respectively. The sample was solved in CDCl3 with tetramethylsilane (TMS) as an internal chemical shift standard.

The number-average molecular weight (Mn) and the weight-average molecular weight (Mw) of PLA were determined by gel permeation chromatography (GPC) equipped with TSKgel SuperMutipore HZ-M*2 column and GPC data processing software. The PLA sample (1 mg/ml) was eluted using tetrahydrofuran (THF) before injection (20 μl), and GPC was operated at a flow rate of 0.35 ml/min at 40°C. Polystyrene with a narrow range of polydispersity (1.03-1.05) was used for calibration. The morphological form of engineered E. coli was characterized using a scanning electron microscope (SEM) on a Hitachi S-4800 instrument. The cells were harvested by centrifugation at 5000 rpm for 5 min and subsequently washed with phosphate-buffered saline (PBS) (pH 7.4) three times. Then, the washed cells were fixed with 2.5% (V/V) glutaraldehyde overnight at 4°C. The fixed cells were washed again with phosphate-buffered saline (PBS) (pH 7.4) three times (30 min each). Afterward, ethanol gradients of 30%, 50%, 70%, 80%, 90%, and 95% (V/V) solutions were used to dehydrate the fixed cells in a sequential way. The cell samples were further dehydrated with 100% ethanol three times. After that, tertiary butyl alcohol was mixed with ethanol in a ratio of 1:1 and pure tertiary butyl alcohol was used to achieve metathesis of ethanol in the cells (Wang et al., 2014). At last, the cells were mixed in with tertiary butyl alcohol and lyophilized for imaging.

The PLA granules in E. coli cells were characterized using a transmission electron microscope (TEM) on a Hitachi H-7650 instrument. The cells were harvested by centrifugation at 5000 rpm for 5 min and subsequently washed with phosphate-buffered saline (PBS) (pH 7.4) three times. Then, the washed cells were fixed with 2.5% (V/V) glutaraldehyde overnight at 4°C. The fixed cells were washed again with phosphate-buffered saline (PBS) (pH 7.4) three times (30 min each). Afterward, ethanol gradients of 30%, 50%, 70%, 80%, 90%, and 95% (V/V) osmic acid was added to fix the cell for 1 h. The fixed cells were washed again with PBS (pH 7.4) three times (30 min each). Afterward, acetone gradient solutions of 30%, 50%, 70%, 80%, 90%, and 95% (V/V) were used to dehydrate the fixed cells in a sequential way. The cell samples were further dehydrated with 100% acetone three times. After that, tert-stabilized alcohol (2:1) was used to achieve metathesis of acetone in the cells (Wang et al., 2014). At last, the cells were mixed in with tert-stabilized alcohol and lyophilized for imaging.
sequential way. The resulting cell samples were further dehydrated with 100% acetone three times. Finally, the cell samples are embedded with Spurr resin for imaging.

**Statistical Methods**
The significance of differences between the mean values of testing samples was compared using Student’s t-test. Differences were considered statistically obvious if \( p < 0.05 \) and significant if \( p < 0.01 \).

**RESULTS AND DISCUSSION**

**Biosynthesis of PLA via Class I PHA Synthase (From Chromobacterium sp. USM2)**
The qualitative \(^1\)H and \(^{13}\)C assay of polymer product (Supplemental Figure S3) confirmed that PLA homopolymer was de novo–biosynthesized from glucose by the engineered strains of *E. coli*, and the \(^1\)H assay also indicated the presence of oligomeric PLA or LA monomer indicated the hydrolysis of PLA during analysis processing. The quantitative comparison of PLA production by different strains (Figure 2) showed that *E. coli* MS5 (with PhaCcs) could produce up to 323.4 mg/L of PLA (0.85% of CDW), obviously higher (\( p < 0.05 \)) than the PLA production (189.5 mg/L, 0.54% of CDW) by the control strain of *E. coli* MS3 (with evolved PhaC1Ps6-19). The results indicated that class I PHA synthase (from *Chromobacterium* sp. USM2) exhibited better performance in the biosynthesis of the PLA homopolymer. This study further compared the \( M_w \) of the produced PLA with the strains of MS5 and MS3 (Table 2). Although the PLA products with two strains present a similar average \( M_w \) (around 21,000 Da), the lower \( M_w/M_n \) value of MS5 indicated that the PLA produced with MS5 has more centralized molecular weight distribution than that of MS3.

As described in earlier studies, only engineered class II PHA synthases were utilized in the biosynthesis of PLA homopolymer and LA-containing copolymers, and the mutation of several residues (E130D, S325T, S477G, and Q481K) can improve their substrate specificities toward LA monomers (Taguchi et al., 2008; Yamada et al., 2009; Jung et al., 2010; Yang et al., 2010; Choi et al., 2016). Class I PHA synthases present higher substrate specificity toward SCL monomers (Zou et al., 2017), but have not been utilized in the biosynthesis of the PLA homopolymer and LA-containing copolymers before. The results of this study confirmed that class I PHA synthase could also be utilized in PLA production (Figure 2). Moreover, the same synthase (PhaCcs) could catalyze the polymerization of 3-hydroxypropionic acid (3HP, an isomer of LA), and the CDW of the produced P (3HP) can reach 40% (Linares-Pastén et al., 2015), indicating that class I PhaCcs shows...
promising substrate specificity toward the SCL hydroxypropionic acids.

**Increased PLA Production by Morphologically Engineered E. coli**

At the time point of 36 h after inoculation, the cells of *E. coli* MS4 (morphological engineering via *sulA*) and MS3 (control strain without *sulA*) were harvested for SEM/TEM analysis. The SEM results revealed that *E. coli* MS4 has an elongated rod cell shape (Figure 3A), which presents a longer cell shape than the control strain of *E. coli* MS3 (Figure 3B). Moreover, TEM results showed that the intracellular PLA granules in *E. coli* MS4 (Figure 3C) occupied larger cell space than in the control strain of *E. coli* MS3 (Figure 3D), indicating the increased PLA production in *E. coli* MS4. The results of fed-batch fermentation (Figure 2) confirmed that *E. coli* MS4 significantly (*p < 0.01*) had higher production of PLA (CDW of 1.96%) than *E. coli* MS3 (CDW of 0.54%). The highest PLA production was achieved by *E. coli* MS6 (contains both *PhaCC* and *sulA*), which can produce up to 950.0 mg/L of PLA in fed-batch fermentation with the CDW of 2.23%.

The significantly increased PLA production in *E. coli* MS4 and MS6 than their control strains of *E. coli* MS3 and MS5 (Figure 2) indicated that the overexpression of the *sulA* gene in *E. coli* strains could morphologically affect the strains to achieve improved production of intracellular polymers. Similar to this study, *E. coli* strains have been morphologically engineered to achieve the increased production of poly(3-hydroxybutyrate-co-4-hydroxybutyrate) (Wang et al., 2014). It has been demonstrated that SulA could bind the tubulin of FtsZ to inhibit the formation of Z loop in the cell division of *E. coli* strains (Pichoff and Lutkenhaus, 2002, 2005; Chen et al., 2012). The SulA/FtsZ interaction was also found in *Pseudomonas* (Chen et al., 2012), indicating that this strategy can be more broadly applied in the biosynthesis of biopolymers by variable chassis strains.

**Fused Pct<sub>Cp</sub>/LdhA Did Not Increase the PLA Production**

As shown in Figure 1, LdhA and Pct<sub>Cp</sub> are two key enzymes in the biosynthetic pathway of lactyl-CoA. In order to supply the increased level of lactyl-CoA for PLA biosynthesis, the fused Pct<sub>Cp</sub>/LdhA enzyme was engineered in *E. coli* MS7 (Supplemental Figure S2). Compared with the PLA production of the control strain of *E. coli* MS4 (CDW of 1.96%), the PLA production of *E. coli* MS7 (CDW of 2.08%) was not apparently increased (*p > 0.05*). In addition, *E. coli* MS7 (containing Pct<sub>Cp</sub> and LdhA fusion enzyme) had a lower dry cell weight (28.9 g/L, 72 h) than *E. coli* MS4 (31.6 g/L, 72 h), which indicated that the presence of fused enzyme exhibits growth stress toward the engineered strain of MS7.

Similar to other fused proteins and enzymes (Yu et al., 2015), the tandem fusion of Pct<sub>Cp</sub> and LdhA can spatially restrain multiple catalytic domains in one fused enzyme. The results of this study indicated that fused Pct<sub>Cp</sub>/LdhA enzyme retained the biocatalytic functions of individual Pct<sub>Cp</sub> and LdhA. However, fused Pct<sub>Cp</sub>/LdhA did not apparently improve the general biosynthesis of PLA, which indicated that the final step (polymerization of lactyl-CoA into PLA by PHA synthase) could be the bottleneck step in the biosynthesis of the PLA homopolymer, as reported by earlier studies (Park et al., 2012; Matsumoto et al., 2018).

**CONCLUSION**

The present study demonstrated that class I PHA synthase from *Chromobacterium* sp. USM2 (*PhaC<sub>Cs</sub>*) is feasible to catalyze the polymerization of the PLA homopolymer from lactyl-CoA. In *de novo* PLA fermentation from glucose, engineered *E. coli* strains having *PhaC<sub>Cs</sub>* present improved PLA production than control strains, which expressed the evolved class II PHA synthase *PhaCl<sub>Pde-19</sub>*. In addition, *sulA*-mediated morphological engineering could enlarge the cell space and further improve PLA production of the engineered *E. coli* strains.

**DATA AVAILABILITY STATEMENT**

The original contributions presented in the study are included in the article/Supplementary Material; further inquiries can be directed to the corresponding author.

**AUTHOR CONTRIBUTIONS**

HZ, MS, and LY conceived and presented the idea. MS, ML, and AY performed the experiment. MS, HZ, and JP wrote the final manuscript. All authors read and approved the final manuscript.

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**SUPPLEMENTARY MATERIAL**

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fbioe.2022.919969/full#supplementary-material
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