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Review

Production of chemicals and proteins using biomass-derived substrates from a *Streptomyces* host

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HIGHLIGHTS

- Production of proteins using *Streptomyces* from biomass-derived substrates.
- *Streptomyces* as a producer of enzymes for degrading biomass polymers.
- *Streptomyces* as a host for production of various chemicals from the substrates.

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ABSTRACT

Bioproduction using microbes from biomass feedstocks is of interest in regards to environmental problems and cost reduction. *Streptomyces* as an industrial microorganism plays an important role in the production of useful secondary metabolites for various applications. This strain also secretes a wide range of extracellular enzymes which degrade various biopolymers in nature, and it consumes these degrading substrates as nutrients. Hence, *Streptomyces* can be employed as a cell factory for the conversion of biomass-derived substrates into various products. This review focuses on the following two points: (1) *Streptomyces* as a producer of enzymes for degrading biomass-derived polysaccharides and polymers; and, (2) wild-type and engineered strains of *Streptomyces* as a host for chemical production from biomass-derived substrates.

Contents

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1. Introduction

Streptomyces strains are aerobic, gram-positive, and mycelia-forming bacteria with high G + C content of their genomes. The strains are distributed in both terrestrial and marine environments. *Streptomyces* is the largest genus in the class actinobacteria, and more than 500 species have been described (Raja and Prabakarana, 2011; Labeda et al., 2012).

Streptomyces is a well-known producer of secondary metabolites via intrinsic metabolic gene clusters, including such classes as polyketides and nonribosomal peptides (Hwang et al., 2014). These metabolites have potential biological activities considered useful for various applications in medicine, veterinary science, and agriculture (Bérdy, 2005; Raja and Prabakarana, 2011). In addition to the production of these secondary metabolites, *Streptomyces* is known to secrete a wide range of extracellular enzymes, and the types of these enzymes are important in various industrial processes: cellulase, xylanase, chitinase, amylase, pectinase, protease, and lipase (Prakash et al., 2013). These enzymes also degrade various biopolymers in nature. *Streptomyces* can incorporate these degrading substrates as nutrients, and the strain can metabolize a wide range of carbon sources. In silico and transcriptional analysis have shown that in *Streptomyces coelicolor*, a model *Streptomyces* strain, the genome encords at least fifty-three potential carbohydrate uptake systems (Bertram et al., 2004). Carbon sources are known to affect various phenotypes, such as secondary metabolite production, enzyme production, cell growth, and morphological differentiation (Jonsbu et al., 2002; Sánchez et al., 2010; Takasuka et al., 2013).

The features mentioned above make *Streptomyces* an attractive host for the production of secondary metabolites and proteins that are useful in industrial applications. Several *Streptomyces* strains have been recently employed as platforms for the production of secondary metabolites and recombinant proteins (Baltz, 2010; Anné et al., 2014). Research into bioconversion using *Streptomyces* has been developed by recent advances in genetic manipulation and system biology tools (Chaudhary et al., 2013; Hwang et al., 2014; Kim et al. 2016; Zhang et al., 2016). Strain manipulation tools such as random mutagenesis, rational manipulation (e.g. regulator manipulation, deletion of competing metabolic pathways, and overexpression of synthetic genes), and optimization of metabolic flux, have all been employed to improve secondary metabolite production. System biology tools such as omics techniques (e.g. transcriptome, proteome, metabolome, and fluxome (analysis of fluxes in metabolic networks)) have significantly aided the understanding of cellular behavior and offered clues for host manipulation. Recent advances in whole-genome sequencing have provided genetic information that has been useful in strain manipulation and in the study via system biology, as well as in genome mining for the identification of secondary metabolite gene clusters and enzymes using heterologous hosts.

Chemical production using renewable sources has recently gained favor because of environmental problems and limited fossil fuel supplies, and the production from microbial hosts using biomass feedstocks as starting substrates has attracted much attention (Becker and Wittmann, 2015). Various biomass-derived substates are readily available: sugars from sugarcane and sugar beets, lignocellulose-derived substrates, starches (e.g. corn and wheat), and vegetable oils (e.g. from palm, soybean, and oilseed) (Wu et al., 2016a). Some substrates are also of economic interest for bioconversion.

The focus of this review is the use of *Streptomyces* for sustainable biotechnological processes derived from biomass feedstocks. This review highlights the following two points: 1) *Streptomyces* is a producer of enzymes for degrading biomass-derived polysaccharides and polymers (particularly plant biomass) into monomers and oligomers; and, 2) wild-type and engineered strains of *Streptomyces* serve as hosts for producing various chemicals from biomass-derived substrates (Fig. 1).

2. Protein production in *Streptomyces*

2.1. Enzyme production in native strains

As mentioned in the introduction, *Streptomyces* intrinsically produces extracellular enzymes which can degrade various biopolymers. Microbes, such as bacteria and fungi, can produce extracellular enzymes for the degradation of lignocellulosic biomass (Saini et al., 2015). *Streptomyces* is well known as a potential producer of enzymes responsible for degradation of biomasses such as lignocellulose and chitin into monomers and oligomers.

Lignocellulose is the most abundant renewable biomass on earth, and it is obtained from agricultural residues, forest residues, crops and cellulosic waste (Parisutham et al., 2014). Lignocellulose is typically comprised of cellulose (30–45%), hemicellulose (15–30%), and lignin (12–25%) (Parisutham et al., 2014). Cellulase is used to degrade cellulose into glucose and oligosaccharides by synergistic degradation of enzymes, such as exoglucanases, endoglucanases, cellobiohydrolases, and β-glucosidases (Saini

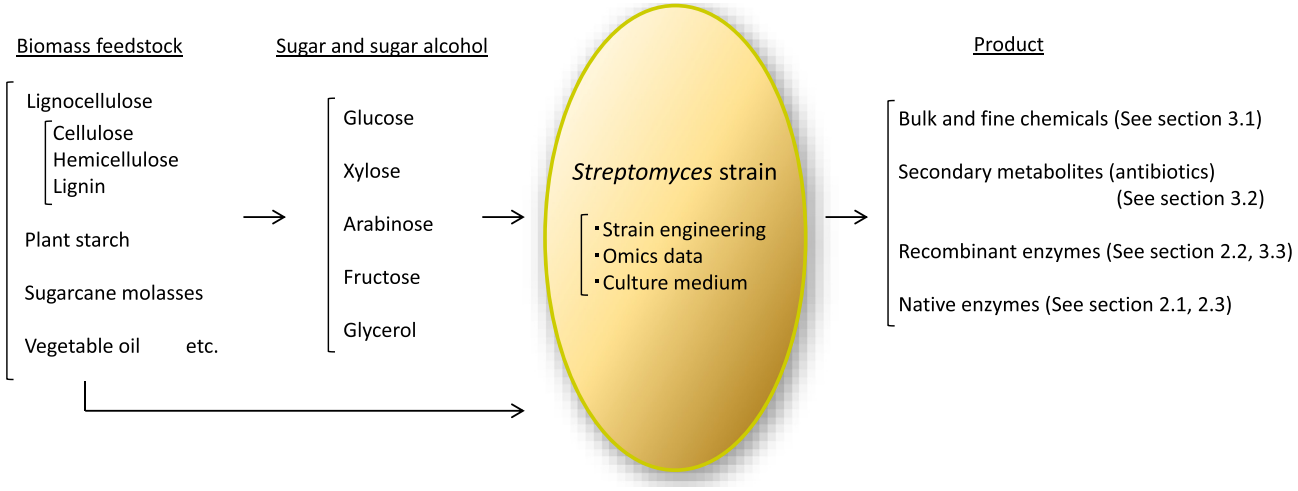

Fig. 1. Diagram of chemical and protein production using biomass substrates in *Streptomyces*.

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