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Biotechnological production of muconic acid: current status and future prospects

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ABSTRACT

Muconic acid (MA), a high value-added bio-product with reactive dicarboxylic groups and conjugated double bonds, has garnered increasing interest owing to its potential applications in the manufacture of new functional resins, bio-plastics, food additives, agrochemicals, and pharmaceuticals. At the very least, MA can be used to produce commercially important bulk chemicals such as adipic acid, terephthalic acid and trimellitic acid. Recently, great progress has been made in the development of biotechnological routes for MA production. This present review provides a comprehensive and systematic overview of recent advances and challenges in biotechnological production of MA. Various biological methods are summarized and compared, and their constraints and possible solutions are also described. Finally, the future prospects are discussed with respect to the current state, challenges, and trends in this field, and the guidelines to develop high-performance microbial cell factories are also proposed for the MA production by systems metabolic engineering.

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Introduction

Many unsaturated dicarboxylic acids, such as important platform chemicals like fumaric acid (Xu et al., 2012) and itaconic acid (Klement and Büchs, 2013), have industrial significance for their double bond and two carboxylic groups and therefore can be polymerized to produce synthetic resins and biodegradable polymers. Another potentially important unsaturated dicarboxylic acid is muconic acid (MA), also known as 2,4-hexadienedioic acid. There are three isomers of MA designated *cis,cis*-MA, *cis,trans*-MA, and *trans,trans*-MA (Bui et al., 2013; Burk et al., 2011). Traditional chemical processes for MA production rely on non-renewable petroleum-based feedstock and high concentrations of heavy metal catalysts (Pandell, 1976; Tsuji and Takayanagi, 1978), or the processes produce a mixture of two isomers (*cis,cis*-MA and *cis,trans*-MA) from expensive catechol (McKague, 1999); consequently, using these processes results in problems of environmental pollution, petroleum depletion, and/or high cost of a separation process. Thus, a sustainable, environmentally friendly and cost-effective biotechnological process based on inexpensive carbohydrate

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raw materials is very desirable. Because of its stereospecific configuration along with the reactive dicarboxylic groups and the conjugated double bonds, MA can undergo a wide variety of reactions as a promising building block or intermediate to produce commodity and specialty chemicals. Such products, including commercially important bulk chemicals such as adipic acid, terephthalic acid, and trimellitic acid, have a wide variety of uses in the manufacture of nylon-6,6, polytrimethylene terephthalate, polyethylene terephthalate, dimethyl terephthalate, trimellitic anhydride, industrial plastics, resins, polyester polyols, food ingredients, pharmaceuticals, plasticizers, cosmetics, and engineering polymers (Fig. 1) (Bui et al., 2012; Bui et al., 2013; Burk et al., 2011; Chen et al., 1992; Coudray et al., 2013; Fink, 2005; Frost et al., 2010, 2013a, 2013b, 2013c; Polen et al., 2013; Schweitzer, 2012). In fact, the worldwide consumption of dimethyl terephthalate was 3.97 million metric tons in 2012 (Bui et al., 2013). MA can also be easily hydrogenated to yield adipic acid, which belongs to the top 50 bulk chemicals (Niu et al., 2002; Weber et al., 2012). With an annual global production of approximately 2.8 million metric tons, adipic acid is a versatile building block for an array of processes in the chemical, pharmaceutical and food industries (Burgard et al., 2011; Cavani and Alini, 2009; Van de Vyver and Román-Leshkov, 2013; Wu et al., 2011).

Currently, the industrial process accounting for total adipic acid production relies on the catalytic oxidation of cyclohexanol or a cyclohexanol/cyclohexanone mixture with an excess of HNO_3. Such a process requires a high energy input and yields large amount of N_2O as by-product, corresponding to 5–8% of the worldwide anthropogenic emissions of N_2O. N_2O is commonly thought to cause global warming, ozone depletion, acid rain, and smog (Bolm et al., 1999; Cavani and Alini, 2009; Van de Vyver and Román-Leshkov, 2013). With regard to the increasing public awareness of environmental protection and sustainable development, conventional industrial processes for such important bulk chemicals production are undesirable, because of their heavy reliance upon environmentally sensitive and non-renewable feedstocks, high-energy input, and propensity to yield undesirable by-products. In the last two decades, industrial biotechnology has made significant advancements due to its attractive advantages, such as sustainability, high selectivity, mild operation conditions, "green" catalysts, renewable feedstocks, and water-phase systems (Hjeresen et al., 2001; Olguín et al., 2012; Sheldon, 2005; Shin et al., 2013; Xu et al., 2007). Thus, biotechnological routes to the precursor MA could provide a promising alternative to the conventional method for adipic acid production (Polen et al., 2013; van Duuren et al., 2011a).

Recently, the development of biotechnological processes for MA production has been pursued with enthusiasm. Many improvements have been made in developing microbial cell factories by construction of artificial biosynthetic pathways and optimizations of metabolic networks. Here, we provide a comprehensive and systematic overview of the existing and emerging biological methods for producing MA. The future prospects are discussed, and the guidelines to develop superior microbial cell factories by systems metabolic engineering are also proposed.

MA production from aromatic compounds

The ortho-cleavage pathway of catechol

Aromatic compounds comprise approximately one-quarter of the Earth's biomass and are the second most widely distributed class of organic compounds in nature (Valderrama et al., 2012). Many aromatic compounds, such as benzoate, toluene, benzene, phenol, aniline, anthranilate, mandelate, and salicylate, are oxidized adaptively by some bacteria with the formation of catechol as the central aromatic intermediate through a variety of ring modification reactions (Harwood and Parales, 1996). The aromatic ring of catechol can be cleaved in two ways, the *ortho*-cleavage pathway and the *meta*-cleavage pathway, depending on the type of bacteria (Vaillancourt et al., 2006; Wells and Ragauskas, 2012). In the catechol *ortho*-cleavage pathway, catechol 1,2-dioxygenase (EC 3.1.11.1, CatA) performs intradiol cleavage of the aromatic ring to yield MA (Fig. 2).

Benzoate is stable, water soluble and non-volatile, and thus easy to handle in a water-phase system (Wang et al., 2001; Yoshikawa et al., 1990). These advantages, together with its fairly low price, make benzoate one of the most common raw materials for MA production. Some microorganisms belonging to the genus *Pseudomonas*, *Arthrobacter*, *Corynebacterium*, *Brevibacterium*, *Microbacterium*, and *Sphingobacterium* were reported to metabolize benzoate via the catechol branch of the β-ketoadipate pathway to produce MA (Table 1). Benzoate is first converted to benzoate diol catalyzed by benzoate 1,2-dioxygenase (EC 1.14.12.10) encoded by *benABC*. Then, the oxidative decarboxylation of benzoate diol to catechol is performed by benzoate diol dehydrogenase (EC 1.3.1.25) encoded by *benD* (Harwood and Parales, 1996). Ring fission of catechol between the hydroxyl groups is catalyzed by CatA encoded by *catA* to form MA, and the latter metabolite is then converted into muconolactone by muconate cycloisomerase (EC 5.5.1.1) encoded by *catB*. Muconolactone is finally converted to tricarboxylic acid cycle intermediates after several more metabolic steps (Fig. 2) (Vaillancourt et al., 2006; Wells and Ragauskas, 2012).

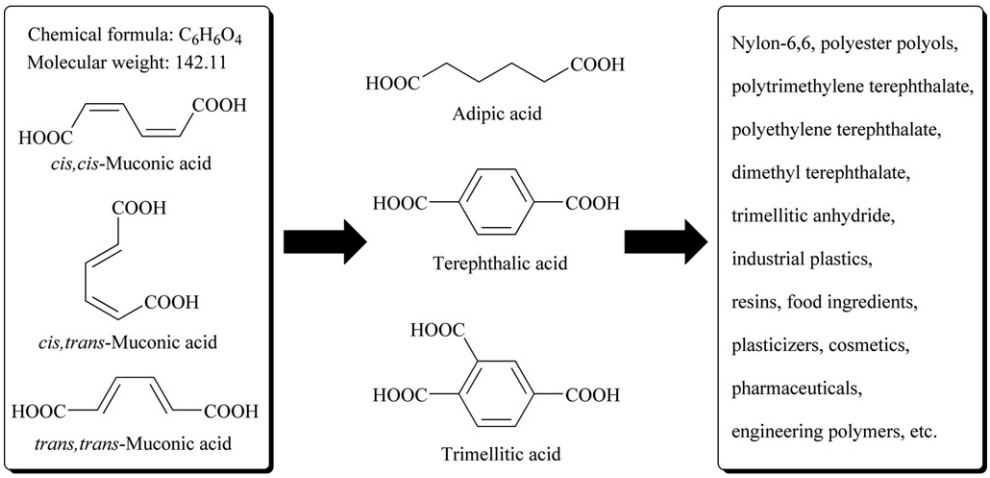

Fig. 1. Summary of the industrial products derived from three isomers of MA.