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Metabolic Engineering and Synthetic Biology – Review

Research progress of the biosynthetic strains and pathways of bacterial cellulose

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Abstract: Bacterial cellulose is a glucose biopolymer produced by microorganisms and widely used as a natural renewable and sustainable resource in the world. However, few bacterial cellulose-producing strains and low yield of cellulose greatly limited the development of bacterial cellulose. In this review, we summarized the 30 cellulose-producing bacteria reported so far, including the physiological functions and the metabolic synthesis mechanism of bacterial cellulose, and the involved three kinds of cellulose synthases (type I, type II, and type III), which are expected to provide a reference for the exploration of new cellulose-producing microbes.

Keywords: Bacterial cellulose, Biosynthesis, Cellulose synthase

Introduction

Cellulose is the most widely distributed and most abundant polysaccharide in nature, with a global annual output of 10^{10}–10^{11} tons (Lavoine et al., 2012). Especially, nanocellulose has become the current research focus due to its nanostructure, high strength, high purity, high biocompatibility, and high biodegradability. The latest evaluation report predicts that the global market value of nanocellulose in 2021 may be amounted to $530 million (Glenn, 2015). Nanocellulose mainly includes nano-microcrystalline cellulose, nanofibrillated cellulose, and bacterial cellulose. Among them, bacterial cellulose produced by microorganisms has the lowest market share but the fastest growth rate, so it has great development potential (Li et al., 2016; Li et al., 2017a; Li et al., 2017b). The main difference between bacterial cellulose and other two types of nanocellulose is that the former is produced by microorganisms, while nano-microcrystalline cellulose and nanofibrillated cellulose are mainly derived from plants. In plant tissues, some components such as cellulose, hemicellulose, lignin, and pectin are usually tightly coupled and difficult to separate directly, so the process of using plants to prepare nanocellulose is more complex and less efficient. The cellulose produced by microorganisms does not contain hemicellulose and other components. Its purity is high, and the content of cellulose can reach more than 99%. In addition, bacterial cellulose is produced by microorganisms, which has a short growth cycle, fast metabolism, and strong reproduction ability. Therefore, the cellulose synthesis efficiency is high, and the relative microbial metabolism pathway is relatively clear, which is more conducive to the regulation of cellulose synthesis.

At present, 30 bacterial cellulose-production strains have been identified. Based on these strains, many studies have been conducted to improve the production of bacterial cellulose by optimizing culture conditions, culture modes, and metabolic engineering strategies. However, due to the characteristics of the bacteria and the fiber itself, the cellulose yield was still low. Table 1 showed the currently reported static fermentation synthesis of bacterial cellulose. The maximum yield of bacterial cellulose did not exceed 20 g/l, which has not yet reached the level of industrial application. Obviously, the screening of strains producing bacterial cellulose based on cellulose-production microorganisms is a fundamental strategy for enriching the types of bacterial cellulose-producing strains and obtaining high-performance bacterial cellulose, which is conduce to the deep development and utilization of bacterial cellulose. This article reviewed the physiological functions of bacterial cellulose, the types of bacterial cellulose producing strains reported so far, and the metabolic synthesis mechanism of bacterial cellulose. It is expected that it can provide a certain theoretical and practical basis for the screening of new bacterial cellulose-producing strains, the acquisition of high-performance and high-yield bacterial cellulose, and the industrial application of bacterial cellulose.

Physiological Effects of Bacterial Cellulose from Microorganisms

Bacterial cellulose is one kind of extracellular polysaccharide which includes homopolysaccharides (such as cellulose, dextran, pullulan, coagulated polysaccharides) and heteropolysaccharides (such as gelatin, xanthan gum) synthesized by microorganisms (Ashjaran, 2013). Bacterial cellulose has a variety of physiological effects such as lowering blood sugar and immunoregulation, which make it can be widely used in food, medicine, and other industries (Fig. 1) (Cheng, 2010; Matsushita et al., 2016).

During static culture, the oxygen content in the culture solution decreases from top to bottom. Bacterial cellulose synthesized in static culture can be arranged to form a cellulose film on the surface of the culture, which can be used as a carrier of aerobic

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Table 1 The Production of Bacterial Cellulose Through Static Fermentation

Strain	Carbon source	Nitrogen source	Additives	T (°C)	pH	Time (days)	Yield (g/l)	Ref
Gluconacetobacter xylinus ATTC 53524	sucrose	Peptone yeast extract	-	30	5		3.83	(Mikkelsen et al., 2009)
Gluconacetobacter hansenii UAC 09	sucrose	-	grape skin	-	-	14	7.47	(Rani et al., 2011)
G. xylinus ATCC 10245	molasses	corn syrup	-	30		6	4.70	(El-Saied et al., 2008)
G. hansenii PJK KCTC 10505BP	glucose	beer fermentation broth	-	30	5	14	13.95	(Ha et al., 2008)
Gluconacetobacter sp.4B-2	sucrose	Peptone yeast extract	-	30	6–7	8	11.98	(Pourramezan et al., 2009)
G. xylinus ATCC 23770	wheat straw hydrolysate	Peptone yeast extract	-	30	5	11	15.40	(Hong et al., 2011)
Acetobacter Xylinum ATCC 23769	glucose	Peptone yeast extract	oligosaccharides	30	3.5	15	15.28	(Ha & Park, 2012)
G. xylinus BCRC 12334	glucose	Peptone yeast extract	lees	30	6	7	10.38	(Wu & Liu, 2012)
G. xylinus ATCC 23770	cotton cloth hydrolysate	Peptone yeast extract	-	30	-	7–14	10.80	(Hong et al., 2012)
Gluconacetobacter Xylinus ATCC 23770	fiber hydrolysate	Peptone yeast extract	-	30	5	7	11.00	(Cavka et al., 2013)
Gluconacetobacter xylinus ATCC 13693	glucose	Peptone yeast extract	lignin sulfonate	28	6	7	16.32	(Keshk & Sameshima, 2006a)

bacteria growth for more convenient contacting with oxygen. The family *Acetobacteraceae* is a typical representative (Raghavendran et al., 2020). On the other hand, bacterial cellulose can also protect the bacteria from the damage of environmental conditions. For example, acetic acid bacteria can produce gluconic acid, acetic acid, and other organic acids in the culture process, which greatly reduces the pH value of the culture medium. Although the acetic acid bacteria have a unique acid resistance mechanism, low pH value will still inhibit the growth of bacteria. The cellulose membrane synthesized at the gas–liquid interface can weaken this effect and protect the bacteria (Raghavendran et al., 2020). Additionally, the cellulose produced by acetic acid bacteria on the surface of rotten fruits can protect it from ultraviolet rays and promote its growth and metabolism (Matsushita et al., 2016).

Bacterial cellulose also plays a vital role in nitrogen fixation or root cancer formation in plant roots participated by *Rhizobium* and *Agrobacterium* (Matsushita et al., 2016). First, the bacterial protein attached to the surface of the plant lectin and the acidic polymer form an unstable complex. Then the bacterial cell produced short-fibrous bacterial cellulose to tightly connect the complex with the plant tissue cells, accelerating cell adhesion. Comparatively, the cellulose-deficient strains have a significantly reduced ability to infect plants. Studies have shown that the cellulose production of *rhizobia* was induced by plant tissues, that is, only when the fungus contacted plant cells (Matsushita et al., 2016). Similarly, some bacteria of *Aerobacter* can also produce cellulose to promote the adsorption of bacteria and plant cells (Chen et al., 2017; Choi & Shin, 2020).

For *Salmonella* and *Escherichia coli* that adhere to the surface of vegetables and fruits, in order to maintain the ability of the bacteria to infect the host, they synthesized cellulose to resist damage from external ultraviolet rays and antibiotics (Römling & Galperin, 2015). In addition, studies have shown that *Salmonella typhimurium* can even produce cellulose to attach to the hyphae of *Aspergillus niger*, while cellulose-deficient strains do not have the ability to attach to fungi (Brandl et al., 2011).

In addition, some microorganisms of *Pseudomonas*, *Achromobacter*, *Alcaligenes*, and *Agrobacterium* can also produce trace amounts of cellulose, causing flocculation of wastewater (Jung et al., 2007). At the same time, some strains of *Sarcina* can produce amorphous cellulose to make cells adhere to each other to facilitate nutrient absorption (Dutta & Lim, 2019). While, the physiological role of cellulose produced by *Rhodobacter*, *Bacillus,* and *Shewanella* is unclear (Liang et al., 2010; Römling & Galperin, 2015).

It was studied that some cellulose-producing bacteria can produce other polysaccharides at the same time. *Shewanella oneidensis* MR-1 can produce mannose during synthesizing cellulose (Liang et al., 2010). *Acetobacter aceti* IF0 3284 will form a polysaccharide composed of glucose and rhamnose (Moonmangmee et al., 2002). However, the physiological effects of these polysaccharides are not clear at present. Most studies have suggested that the production of soluble polysaccharides is not directly related to bacterial cellulose synthesis (Gorgieva & Trček, 2019).

Natural Bacterial Cellulose Produced by Microorganisms

At present, it was studied that a variety of bacteria can synthesize extracellular cellulose. The cellulose microfibrils synthesized by *Rhizobium* and *Agrobacterium* could be involved in the process of cell adsorption to plant host, but the yield was extremely low. The bacterial cellulose that has high yield and can form significant cellulose film is mainly synthesized by *Komagataeibacter*, *Acetobacter*, *Gluconacetobacter*, *Gluconobacter,* and *Asaia* in *Acetobacteriaceae*, as well as the *Bacillus*, *Leifsonia*, *Salmonella*, *Erwinia*, *Enterobacter*, *Pseudomonas,* and *Shewanella* in non *acetobacteriaceae*.

Bacterial Cellulose Producing Strains in *Acetobacteriaceae*

Characteristics of bacterial cellulose produced by different genera are different. *Komagataeibacter* differentiated from *Gluconobacter*

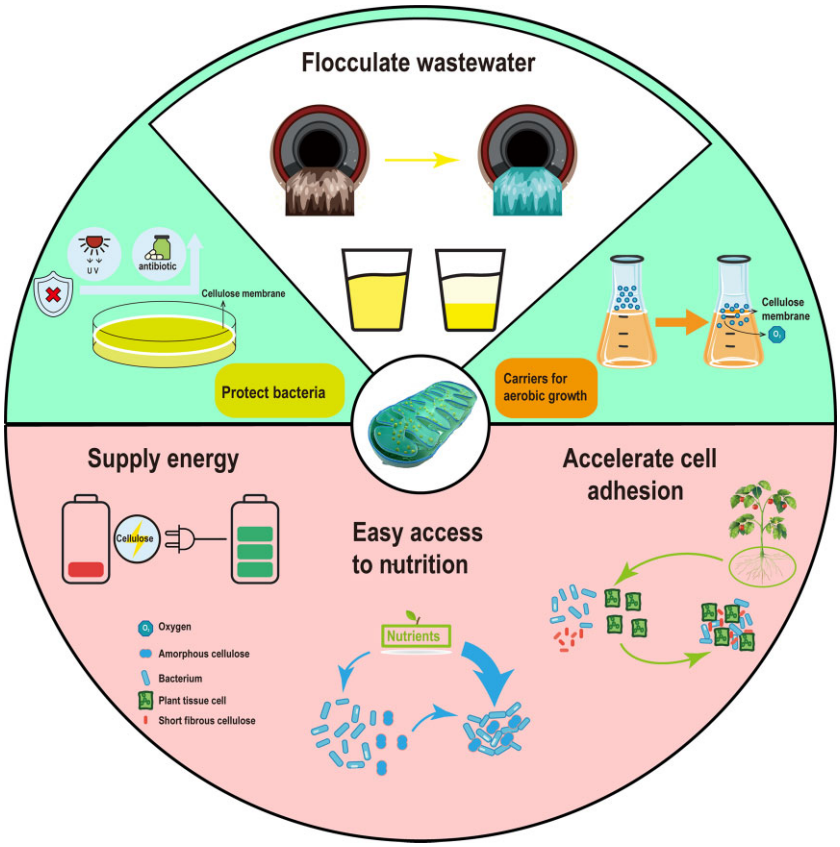

Fig. 1. Functional applications of bacterial cellulose in various fields.

was proposed and established by YAMADA Y in 2012 (Yamada et al., 2012). Typical species of which was *Komagataeibacter xylinus* that was the first microorganism found to be able to produce cellulose. There are currently 14 species of bacteria in *Komagataeibacter*, of which five species (*Komagataeibacter hansenii*, *Komagataeibacter europaeus* SGP37, *Komagataeibacter oboediens*, *Komagataeibacter intermedius* and *Komagataeibacter saccharivorans*) cannot produce cellulose. However, recent researches had found that these five species from other sources, *K. hansenii* (Uzyol & Saçan, 2017), *K. europaeus* SGP37 (Dubey et al., 2017), *K. oboediens* (Wei-hua et al., 2009), *K. intermedius* (Lin et al., 2016) and *K. saccharivorans* (Hassan et al., 2015) could produce obvious cellulose membranes, indicating that the microorganisms in this genus have the potential to produce bacterial cellulose.

There were 24 strains of *Acetobacter* at present, which were mainly used to produce vinegar. Among them, *Acetobacter aceti* MTCC 2623 (Dayal et al., 2013), *Acetobacter lovaniensis* HBB5 (Çoban & Biyik, 2011), *Acetobacter okinawensis* BIT04 (Mugesh et al., 2016), *Acetobacter orientalis* strain dfr-4 (Ramana & Batra, 2015), *Acetobacter orleanensis* NCIB 12584 (Byrom, 1990), *Acetobacter pasteurianus* NCIB 7029 (Byrom, 1990), and *Acetobacter tropicalis* SKU1100 (Ali et al., 2011) produced obvious cellulose membranes, but this genus were genetically unstable and had a higher probability of defects in the ability to produce cellulose (Azuma et al., 2009).

Gluconacetobacter can oxidize gluconate and acetate, in which *Gluconacetobacter entanii* (Velasco-Bedrán & López-Isunza, 2007), *Gluconacetobacter liquefaciens* (Aydin et al., 2010), *Gluconacetobacter persimmonis* (Hungund & Gupta, 2012), and *Gluconacetobacter sacchari* (Gomes et al., 2013; Trovatti et al., 2011) could produce cellulose membranes. Besides, *Gluconacetobacter entanii* (Velasco-Bedrán & López-Isunza, 2007) and *Gluconacetobacter diazotrophicus* (Serrato et al., 2013) in this genus also produced other types of noncellulosic extracellular polysaccharides. *Gluconobacter* mostly grows in an environment rich in sugar, whose tolerance of glucose up to 10%. It is mainly used in the synthesis of vitamin C and miglitol (Shinjoh & Toyama, 2016), enzyme research (Macauley et al., 2001), and the development and application of sensors (Svitel et al., 2006). There are currently 14 bacteria in this genus, of which *Gluconobacter cerinus* (Mugesh et al., 2016), *Gluconobacter oxydans* TQ-B2 (Shiru Jia et al., 2004), and *Gluconobacter uchimurae* GYS15 (Lee et al., 2016) produced cellulose, but there were few studies on them.

Asaia bogorensis from *Asaia* produced cellulose membranes with a fiber diameter of 5–20 nm. The membrane had poor strength and the yield was low, but it was still significantly higher than that of *Rhizobium* and other microorganisms. This may be due to the high content of Iβ-cellulose in the fiber structure (Kumagai et al., 2011).

Bacterial Cellulose Producing Strains in Non *Acetobacteriaceae*

The above cellulose-producing bacteria all belong to gram-negative *Acetobacteraceae*. They are characterized by obligate aerobic, ability to oxidize ethanol to acetic acid, decompose calcium carbonate to produce a transparent circle, and tolerate lower pH (Aydın & Aksoy, 2014). Moreover, there were also other types of microorganisms capable of producing cellulose membranes. For example, *Bacillus amyloliquefaciens* can produce the substance with structures similar to that of cellulose, which were membrane-like under static conditions, suspending on the surface of solution,

and spherical under dynamic conditions (Zhang & Nakajima, 2015). *Leifsonia* sp. CBNU-EW3, a gram-positive bacteria screened from earthworms, can produce bacterial cellulose membrane during static culture as well. The optimum pH for producing cellulose membrane of this bacterium was acidic and its production time was long, but the membrane-producing ability was not much different. The fiber structure in the cellulose membrane was uneven in thickness (Velmurugan et al., 2015). *Salmonella enterica* is a short rod-shaped strain producing bacterial cellulose. The fiber's microstructure produced was similar to honeycomb, and the bacteria was located in the center of honeycomb. This may be explained by that it had a different transposon for producing cellulose making the fiber diameter and branch type were completely different from *K. xylinus* (Jahn et al., 2011). The bacteria cellulose synthesized by *Dickeya dadantii* 3937 had a fiber network structure similar to *Acetobacteraceae* and had the same membrane-production transposon. However, its fiber was beaded, which may be caused from its unique third type of secretory system (T3SS) (Jahn et al., 2011). The bacterial cellulose-production capabilities of *Salmonella enterica* and *Dickeya dadantii* were analogous to *K. xylinus*. So, they also had significant development potential.

Enterobacter sp. CJF-002 and *K. xylinus* ATCC23769 had similar membrane-producing genes. For this reason, a similar cellulose network structure could be generated. Since the membrane production process in *Enterobacter* sp. CJF-002 belonged to growth coupling type without obvious lag period, it had slightly higher membrane production speed and denser cellulose network structure than those of latter. Meanwhile, *Enterobacter* sp. CJF-002 was *Enterobacter* with the highest membrane yield currently reported, having considerable potential for industrial application (Sunagawa et al., 2012). Moreover, *Enterobacter* is a facultative anaerobic microorganism that could generate enough energy for fiber synthesis under both anaerobic and aerobic conditions (Ji et al., 2016). *Escherichia coli* 1094 was an isolated strain with good ability to produce cellulose, in which a new bacterial cellulose synthesis regulation pathway involving the GGDEF domain protein YedQ was discovered. The study pointed out that besides the CsgD/AdrA regulatory pathway, both CsgD-independent/YedQ-dependent and CsgD-independent/YedQ-independent pathways existed in *E. coli*, which meant that there were abundant alternative cellulose pathways in *E. coli* (Re & Ghigo, 2006).

Shewanella oneidensis MR-1 was a facultative anaerobic bacterium. During aerobic growth, its bacterial metabolism was active and it produced a significant biofilm on the surface of culture medium (Liang et al., 2012). Besides, the bacterium also produced mannose when producing membranes, and the membrane production was related to some metal ions (Liang et al., 2010). In addition, *Pseudomonas* sp. RV14, which is a gram-negative bacterium, produced bacterial cellulose as well, but the membrane production capacity was slightly lower than *Gluconacetobacter* sp. RV28 (Rangaswamy et al., 2015).

Other Potential Bacterial Cellulose Producing Chassis Cells

Escherichia coli has developed into a highly potential cell factory for accomplishing bacterial cellulose production because of its rapid growth, clear genetic background, mature genetic engineering operation tools, and stable plasmid system. In addition to the use of its natural synthetic pathway to produce bacterial cellulose, there are many studies using this strain as chassis cells for heterologous bacterial cellulose producing or key synthetic enzyme mechanism study. A functional and stable bacterial cellulose production system was established in *E. coli* by recombinant expression of both the bacterial cellulose synthase operon (bcsABCD) and the upstream operon (cmcax, ccpAx). Comparing with the bacterial cellulose produced by *Gluconacetobacter hansenii*, the length and diameter of bacterial cellulose were effectively increased (Buldum et al., 2018). The crystalline structure of bacterial cellulose was improved by heterologous expression of the cellulose synthase subunit D (bcsD) gene of *Gluconacetobacter xylinus* BPR2001 in wild type *E. coli* Nissle 1917, and its crystallization index was increased by 17% compared to that of the wild type (Sajadi et al., 2017). In addition, the cellulose production was increased by heterologous expression of bcsA and B genes from *Gluconacetobacter xylinus* in *E. coli* Nissle 1917 without affecting its crystallization index (Sajadi et al., 2019). Recently, engineered gene circuit kinetic modeling was designed and applied in cellulose biosynthesis prediction in *E. coli*, providing important data support for the development of cell factories for bacterial cellulose synthesis (Buldum et al., 2020). Based on the cellulose-producing *E. coli* 1094 strain as a model, the structure–function relationships between core and accessory Bcs subunits were analyzed, which showed that regulatory Bcs components contribute to secretion by affecting both the initial assembly and subsequent stability of the system and provide additional inputs for function regulation by the activating second messenger c-di-GMP (Krasteva et al., 2017). Tomoya Imai et al. expressed CesA and CesB of *Gluconacetobacter xylinus heterologously* in *E. coli*, and synthesized extremely fine cellulose with nonnatural crystalline structure. It was showed that *E. coli* can be used as a platform strain for functional analyses of cellulose synthase and for seeding new nanomaterials (Imai et al., 2014).

There was no report about cellulose production in fungi at present. This was probably because fungi can produce cellulases to break down fibrous substances in nature for growth. However, *Candida* spp. was able to produce biofilms composed of mannose and glucose for flocculation and adhesion. Moreover, the biofilm could significantly increase the resistance to antibiotics (Chandra et al., 2001). Additionally, *Pneumocystis* spp. produced biofilms with dextran as the main structure (Cushion et al., 2009). Besides, fungi often produced various extracellular polysaccharides. For example, the fruit bodies of *Pleurotus eryngii*, *Flammulina velutipes*, and *Agaricus edodes* contained β-glucan, trehalose, and other soluble polysaccharides; *Flammulina velutipes* produced arabitol as well (Zhu et al., 2021). Regarding *Aspergillus* sp. Y16, isolated from marine mangrove plants, its extracellular polysaccharides comprised mannose and galactose; while the fermentation broth of *Aspergillus versicolor* LCJ-5–4 contained neutral heteropolysaccharides and dextran, both were made up of glucose. Meanwhile, the extracellular polysaccharides of *Penicillium griseofulvum* isolated from the submarine matrix consisted most of galactomannans (Chen et al., 2013).

Synthetic Pathways of Bacterial Cellulose in Microorganisms

The biosynthesis of bacterial cellulose contains three steps, including uridine diphosphate glucose synthesis, cellulose molecular chain synthesis, and cellulose crystallization and polymerization.

Synthesis of Uridine Diphosphate Glucose

In the microbial cell, the carbon source from the culture medium can be converted into uridine diphosphate glucose (UDP-glucose) through a series of enzymatic reactions, which is an important

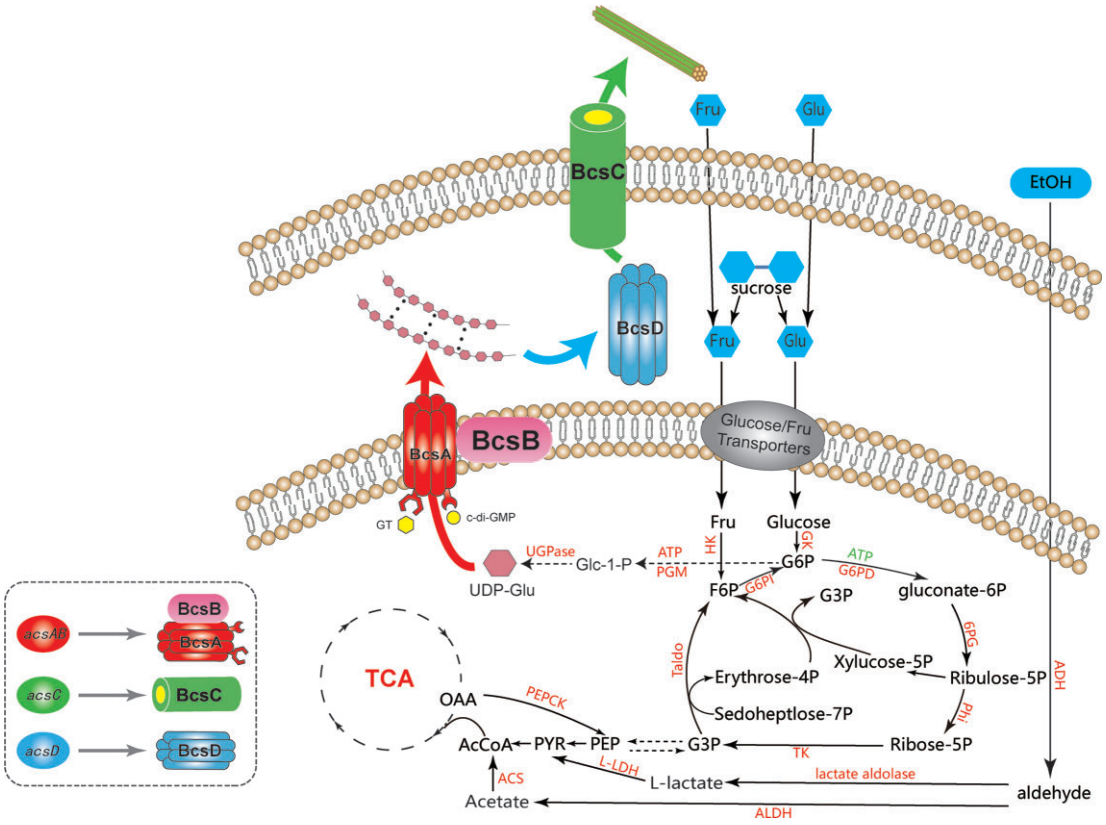

Fig. 2. The synthesis of bacterial cellulose via the cellulose synthase including BcsAB, BcsC, and BcsD subunits. First, different kinds of carbon sources were utilized to form the precursor UDP-glucose of bacterial cellulose (black line), then BcsAB subunit expressed by the gene *acsAB* catalyzed the synthesis of β-1,4-glucan chains (red line), further BcsD subunit secreted by the gene *acsD* is mainly involved in the crystallization to yield the subfibrils with the diameter of 1.5 nm (blue line), and then discharging from the adventitia through BcsC subunits to finally aggregate to form a single fiber with a diameter of 75 nm (green line). PGM, phosphoglucomutase; UGPase, UDP-glucose pyrophosphorylase; GK, glucokinase; HK, hexokinase; ACS, Acyl-CoA synthetase; PEPCK, phosphoenolpyruvate carboxykinase; G6PD, glucose-6-phosphate dehydrogenase; 6-PG, 6-phosphogluconate dehydrogenase; Taldo, transaldolase; TK, transketolase; Phi, ribosephosphate isomerase; ALDH, acetaldehyde dehydrogenase; ADH, alcohol dehydrogenase; L-LDH, L-lactate dehydrogenase; G6PI, glucose-6-phosphate isomerase; GT, glycosyltransferase.

precursor for the synthesis of bacterial cellulose. Taking *K. xylinus* utilizing glucose as an example, since the bacteria does not contain glycolytic pathway (EMP), glucose molecules produced energy and intermediate metabolites for the growth of bacteria through pentose phosphate cycle (HMP) and tricarboxylic acid (TCA) cycle. At the same time, glucokinase, phosphoglucomutase, and UDP-glucose pyrophosphorylase catalyzed glucose to form UDP-glucose, the precursor of cellulose synthesis (Fig. 2). In the above process, phosphoglucose dehydrogenase in HMP determines whether the bacteria use glucose for growth or cellulose synthesis. (Karlstaedt et al., 2020). In addition, UDP-glucose pyrophosphorylase, located in the cytoplasm, is a key enzyme in the synthesis of UDP-glucose. In the absence of this enzyme, cellulose cannot be synthesized due to the lack of precursors. Studies have shown that in high-yield cellulose strains, the UDP-glucose pyrophosphorylase activity is higher, but there are large differences among different strains (Kornmann et al., 2003).

Under anaerobic conditions, there are similar glucose metabolism and UDP-glucose synthesis pathways in other types of cellulose-producing microorganisms as well, such as the facultative anaerobic *Enterobacter* sp. FY-07 (Ji et al., 2016). Regarding other non-glucose carbon sources, such as sucrose, fructose, and ethanol, they are converted into UDP-glucose through TCA, gluconeogenesis, etc. entering the metabolic network (Matsushita et al., 2016; Velasco-Bedrán & López-Isunza, 2007).

Synthesis of Cellulose Molecular Chains

Under the function of cellulose synthase, UDP-glucose is catalyzed to form β-1,4 glucan chains, that is, cellulose microfibrils.

Earlier studies believed that cellulose synthase was a glycosyltransferase that plays a major role in the formation of cellulose molecular chains. The enzyme is located on cell membrane, which is a typical membrane-bound protein. In *K. xylinus*, the optimal reaction temperature of this enzyme was 30°C and the optimal reaction pH was 7.5–8.5. Also, its activity depends on Mg^{2+} (Lin & Brown Jr, 1989). The latest research showed that the enzyme was a protein complex containing multiple subunits, including BcsA, BcsB, BcsC, and BcsD (Fig. 2). The functions of BcsA and BcsB subunits are the same in most bacteria, which were used for the synthesis of cellulose *in vitro* alone. Other subunits vary from different strains, regulating the activity of cellulose synthase and cellulose yield by affecting cellulose synthesis, regulation, and secretion. What's more, these auxiliary subunits may have an important impact on the physiological effects of cellulose; for example, biological nitrogen fixation (Römling & Galperin, 2015).

Cellulose synthase is expressed by an operon gene set. Taking *G. hansenii* ATCC 53582 as an example, its operon contains *acsAB*, *acsC*, *acsD*, *cmcax*, *ccpAx*, and *bglxA*, among which *acsABCD* are mainly related to the catalytic secretion of cellulose. While *cmcax* encodes endo-β-1,4-glucanase, *bglxA* encodes β-glucosidase, both of which are cellulases. The function of *ccpAx* is unknown. There's

a possibility that it is related to the distribution and arrangement of various subunits of cellulose synthase. When this subunit is lacking, it will disturb the structure of cellulose synthase and then affect the production of cellulose (Florea et al., 2016; McManus et al., 2016). Other species of membrane-producing bacteria may contain different operon genes to encode different cellulose synthase complexes. Among them, five subunits of cellulose synthase complexes are called type I cellulose synthase, including BcsA, BcsB, BcsC, BcsD, and BcsZ subunits. The typical representative is *K. xylinus*. The complex containing BcsA, BcsB, BcsC, BcsE, and BcsZ subunits is called type II cellulose synthase, which is typically represented by *E. coli*. The complex of BcsA, BcsB, BcsK, and BcsZ subunits is called type III cellulose synthase, which is typically represented by *Agrobacterium tumefaciens* (Römling & Galperin, 2015). However, there may be more than two cellulose synthases complexes existed in one bacterium. For example, *Enterobacter* sp. FY-07 contains the above three cellulose synthase operons, which expresses type I and type II cellulose synthase. Among these three operons, only one that secretes type I cellulose synthase is necessary for cellulose production, and this operon contains only four genes of *acsABCD* (Florea et al., 2016). In contrast, *G. hansenii ATCC* 53582, which is a high-yield cellulose strain, contains two different type II cellulose synthase operons in addition to the type I cellulose synthase operon, suggesting that these two newly discovered operons may be related to high-yield cellulose (Florea et al., 2016).

Currently, the crystal structure of BcsA-BcsB in *Rhodobacter sphaeroides* has been obtained (Morgan et al., 2013). BcsA subunit contains eight transmembrane components and two cytoplasmic binding moieties in this complex; the latter involves glycosyltransferase and c-di-GMP binding domain. While BcsB is in periplasmic space and anchored to cell membrane by a transmembrane helix. Structurally, the complex is a channel extending from the glycosyltransferase across the membrane to the periplasmic space. The size of this channel allows several glucoside units to pass, indicating that the synthesis of extracellular cellulose may take place here (Römling & Galperin, 2015). BcsA-BcsB is the most important part for catalyzing cellulose synthesis. All cellulose-producing microorganisms include these two subunits. Studies have been made to separate this enzyme complex for catalyzing cellulose synthesis *in vitro* (Basu et al., 2016; Basu et al., 2017). Meanwhile, the gene encoding the enzyme complex is also recombinantly expressed in *E. coli* to synthesize cellulose (Imai et al., 2016).

BcsC is in periplasmic space, an N-terminal α-helical structure consisting of 34 peptides repeat sequence and a C-terminal similar to β-barrel structure. There's a chance that the protein is related to peptidoglycan and other cellulose synthase complex, involved in the extracellular secretion of glucan. This subunit exists in a variety of bacteria, such as *K. xylinus*, *Dickeya dadantii*, *Burkholderia phymatum*, *Salmonella enterica*, *Pseudomonas putida*, *Burkholderia mallei*, and *Chromobacterium violaceum* (Römling & Galperin, 2015). While BcsK subunit in *A. tumefaciens* contains another different 34-peptide repeat sequence, which is expressed by the third type bcs operon. BcsD is also a cylindrical polymer formed by oligomeric periplasmic proteins, with a diameter of about 90 Å, which can accommodate the simultaneous synthesis of four different glucan molecular chains (Hu et al., 2010). BcsH is unique to *Komagataeibacter* and is necessary for the activity of BCS enzyme complex. It interacts with BcsD in periplasmic space, which is likely to be the reason for high cellulose production of *K. xylinus* (Römling & Galperin, 2015).

The complex of BcsQ and other subunits in *Enterobacter* such as *E. coli* is located at both ends of cell. As an adenosine triphosphatase, it is possible to connect with cell localization and cell adhesion (Le Quéré & Ghigo, 2009). *Escherichia coli* divide abnormally when the gene is inactivated, and the chromosomes divide incompletely and produce special filamentous cells (Kim et al., 2002).

BcsZ is an endo-1,4-β-xylanase, whose existence may be used to regulate the synthesis of cellulose. But the enzyme cannot break down network-shaped or even amorphous bacterial cellulose. It is because both have a certain degree of crystallinity (Basu et al., 2016). However, destroying the enzyme gene will reduce the yield of cellulose produced by *K. xylinus* and affect the length and film-forming ability of *Rhizobium leguminosarum* microfibers (Robledo et al., 2012).

BcsE is secreted by the second type of *bcs* operon and exists in many bacteria such as *E. coli*, *Salmonella enterica*, and *Klebsiella pneumoniae*. BcsE is unnecessary for cellulose synthesis in *S. enterica*, but is necessary to increase cellulose production. The reason is probably that the subunit also has a c-di-GMP domain, making it a second pathway for cellulose synthesis (Fang et al., 2014).

In general, taking type I cellulose synthase as an example, BcsAB subunit expressed by the gene *acsAB* is mainly responsible for catalyzing the synthesis of cellulose microfibrils. While BcsD subunit secreted by the gene *acsD* is mainly involved in the crystallization of subfibrils and discharging from the adventitia through BcsC subunits. At the same time, cellulose synthesis is regulated by other cofactors such as c-di-GMP, ATP, and Mg^{2+}. The second messenger c-di-GMP is essential for cellulose synthesis, which activates the BcsAB subunit to initiate the extension of glucan chain (Florea et al., 2016). Also, the synthesis of second messenger requires the participation of energy produced by cell metabolism, so that the production of cellulose is organically linked to the energy metabolism of bacteria (Ji et al., 2016). Additionally, the synthesis of cellulose must have the presence of Mg^{2+}. When ethylenediamine tetraacetic acid is added to chelate metal ions, the catalysis is also impossible due to the dependence of BcsAB on Mg^{2+} (Basu et al., 2016).

Crystallization and Polymerization of Cellulose

Bacterial cellulose is expelled from the cell membrane after intracellular glucan chains synthesis, polymerization, and crystallization. In *K. xylinus*, cellulose synthase is distributed along the long axis of cell. There were about 50 microporous sites in each cell that secrete and excrete cellulose (Fig. 2), whose cellulose synthesis rate was about 2 μm·min^{-1} (Ullah et al., 2016a). Based on existing research, BcsD subunit in the complex is mainly responsible for the crystallization of glucan chain, while BcsC subunit is responsible for the efflux of crystalline cellulose.

Generally, the secretion and assembly of cellulose are principally performed by the following steps: First, 10–15 β-1,4-glucan chains catalyzed by BcsAB subunit are combined by Van der Waals forces to form subfibrils with a diameter of about 1.5 nm. The procedure is mainly regulated by BcsD subunit. Then these synthesized subfibrils are discharged out of the cell through BcsC subunits (micropores) (Nicolas et al., 2021). Relying on hydrogen bonds between molecular chains, the subfibrils aggregate to a diameter of 5–8 nm microfibers. The microfibers form a single bacterial cellulose fiber with a diameter of 75 nm through hydrogen bonds again.

If lack of BcsC and BcsD subunits in this process, only short amorphous type II cellulose can be obtained *in vitro*, although the glucan chains still polymerized and crystallized. While, naturally synthesized bacterial cellulose is mostly type I cellulose, indicating the importance of BcsD subunits in regulating the synthesis

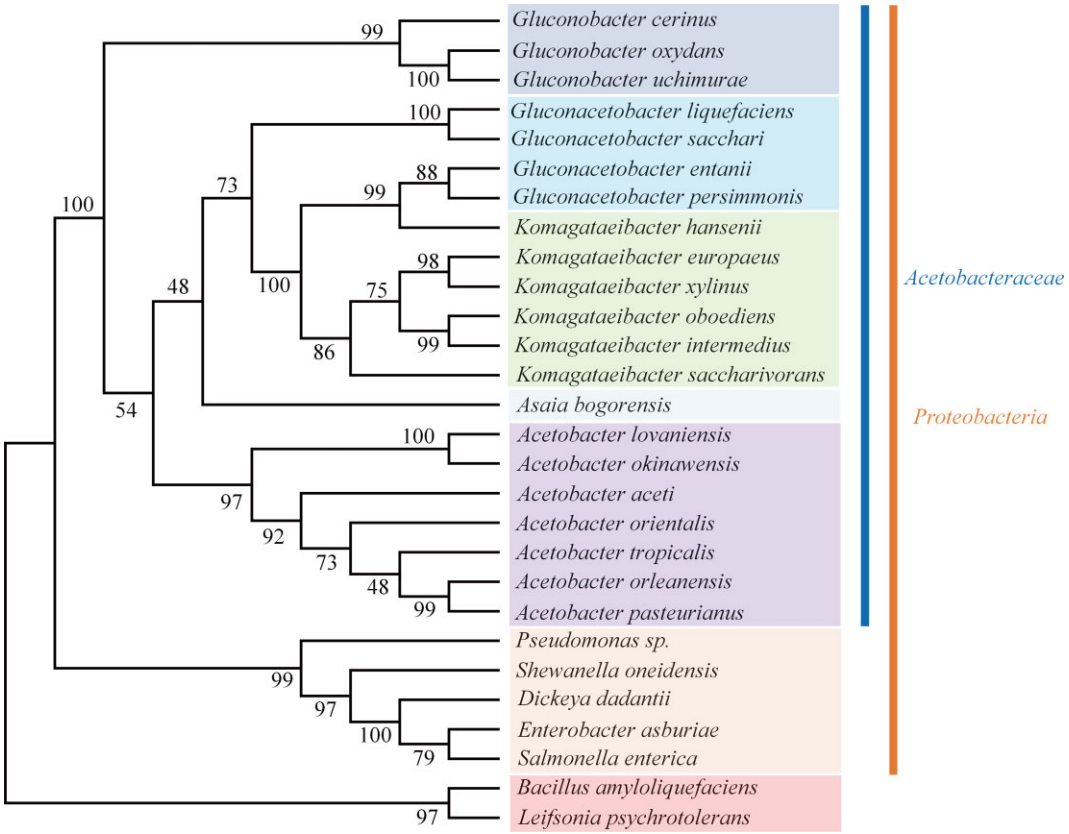

Fig. 3. Phylogenetic relationships of cellulose-producing microorganisms. The phylogenetic tree based on the 16S rRNA sequences was constructed using the unweighted pair group method with arithmetic means (UPGMA) method. Numbers above branches show bootstrap values (%) derived from 1,000 replications.

of subfibrils (Basu et al., 2016). Besides, dynamic culture method interfered with the crystallization and form microfibers with smaller diameters, which was conducive to the emergence of Iβ cellulose (Heßler & Klemm, 2009).

Discussion

Bacterial cellulose is a class of glucose-monomer-based nanolinear molecules produced by microorganisms. The exit of bacterial cellulose can promote the adhesion of bacteria to plant cells and protect the microorganisms from external ultraviolet rays and antibiotics. The characteristic structure of the bacterial cellulose endows it with exceptional physicochemical properties and mechanical features including high purity, high crystallinity, high tensile strength, high water-holding capacity, good biocompatibility, good biodegradability, and nontoxic features. Although its bioavailability is rather low, bacterial cellulose is widely applied in fields of food, cosmetics, biomedical devices, textiles, immobilization, and electronics.

Currently, nanocellulose research develops rapidly, the ever-increasing demand of cellulose has also increased the consumption of plant as a raw material leading to environmental issues. In addition, it is complicated and inefficient to separate the nanocellulose with hemicellulose and other components in plants. The application of bacterial cellulose in future is more advantageous than plant cellulose because the process is efficient and controllable, with high purity of the products. However, bacterial cellulose has the lowest market share among the whole nanocellulose. There are three main reasons for restricting the development of bacterial cellulose: (1) few strains producing cellulose; (2) high production costs; and (3) low cellulose yield.

Strain is a critical factor in microbial industry. Herein, we have reviewed the strains producing bacterial cellulose. Up to now, only 30 species of bacteria were reported to have the ability to produce cellulose (Fig. 3). Among them, only two species of bacteria belong to gram-positive bacteria, the other 28 species of bacteria are derived from *Proteobacteria*, of which 23 species of bacteria belong to *Acetobacteraceae*. It was reported that there were 16 genera, 84 different bacteria in *Acetobacteriaceae* (Komagata et al., 2014). Only five genera bacteria in *Acetobacteriaceae* can synthesize cellulose. It should be noted that the small number of cellulose-producing strains limited the deep development and further utilization of bacterial cellulose. In general, microorganisms are found virtually everywhere, with abundance varieties, strong adaptability, and easy mutation. On the other hand, the most of the found cellulose-producing strains are mainly from *Proteobacteria* (Vu et al., 2009), the largest Phylum of bacteria, which implied the potential possibility of developing more cellulose-producing strains. Therefore, investigating the potential microbes for synthesizing cellulose in nature will be very interesting.

Moreover, the expensive investment resulting from nutrient components and massive power demand has made market price of bacterial cellulose as high as $150 per kilogram (dry weight). Usually, the fermentation process of cellulose-producing bacteria is mostly carried out at 28–30°C, which needs temperature control systems to maintain the growth. One possible solution may come through high temperature fermentation technology employing the thermotolerant cellulose-producing species. For example, the *Komagataeibacter xylinus* MSKU 12 and *Komagataeibacter oboediens*

R37-9, developed in Thailand, were able to grow and effectively produce cellulose under high-temperature conditions (Naloka et al., 2020; Taweecheep et al., 2019). Therefore, the fermentation of the thermotolerant bacterial strain is expected to become one of the most economic methods, which increases the fermentation rate, but reduces cooling costs and operational costs.

Besides the high cost of the process, the main drawback for industrial bacterial cellulose production is low productivity. The highest reported cellulose yield is currently lower than 20 g/l, which is attributed to two reasons. On the one hand, the biosynthesis of cellulose is closely related to central carbon metabolism and energy metabolism of the bacteria, which significantly affects the activities of key enzymes in bacterial cellulose synthesis, such as phosphoglucose dehydrogenase. On the other hand, the bacteria are known to form cellulose pellicles on the surface of the medium, this means the production of cellulose depends on the width of surface area of the culture and the transfer efficiency of oxygen supply. A solution might emerge from the approach of screening a variety of microorganisms capable of producing cellulose. Such an approach would aim at the isolation of hitherto unknown strains and novel genes or enzymes involved in cellulose biosynthesis. To further improve the cellulose productivity, metabolic engineering and process engineering will be applied. Introduction of the synthesis genes, modification of the key enzymes, and regulation of the metabolite will be useful and effective for enhanced production. With respect to fermentation protocols, it is critical to design reactor and optimize reactor conditions such as nutrient selection, temperature, pH, agitation speed, etc.

The development of new species would increase the option of choosing cellulose-producing strains and enrich the genes and enzymes of the biosynthesis pathway, which can provide many strategic choices for metabolic engineering. For example, in order to reduce the major by-products gluconic acid, a glucose dehydrogenase (Gdh) deletion expression strain of *Gluconacetobacter xylinus* strain BPR2001 was acquired to increase the carbon source flow of synthetic cellulose; and the capacity that recombinant strain transformed glucose to synthesize cellulose was 1.7 times than that of wild-type strains (Shigematsu et al., 2005). The introduction of sucrose synthase and hemoglobin into cellulose-producing bacteria can also promote the production of cellulose. After the introduction of sucrose synthase gene, the cells can directly use sucrose to synthesize UDP-glucose, improving the efficiency of cellulose synthesis and avoiding the accumulation of UDP (Nakai et al., 1999). The recombinant expression of hemoglobin gene in Acetobacter *xylinum* BCRC12334 can promote the ability of oxygen uptake, especially in hypoxic environment. Consequently, the cellulose yield of the bacteria has doubled (Chien et al., 2006). In addition, introduction of the cellulose synthase genes gxcesA, gxcesB, and diguanylate cyclase genes from *G. xylinus* JCM9730 into *E. coli* JW5665 has successfully accomplished the cellulose synthesis in *E. coli* (Imai et al., 2016). Overall, with the exploitation of cellulose-producing microbes, we can select the suitable expression hosts, simplify the metabolic pathways, optimize the main catabolism process, and improve the properties (enzyme activity, stability, etc.) of key enzymes to overcome the challenges of producing cellulose.

Furthermore, the production of bacterial cellulose can be increased through process engineering, such as modulating the culture medium, culture mode, and optimizing cell-free culture systems. In terms of culture medium, carbon source, nitrogen source, and additives directly affect the production of bacterial cellulose. Glucose, sucrose, and mannitol are the most used carbon sources. In order to reduce the cost, researchers attempted to produce cellulose from various alternative substrates, especially agro-wastes generated from fruit processing such as molasses (Gama et al., 2016; Keshk et al., 2006), bagasse (Keshk & Sameshima, 2006b), pineapple residue (Zakaria & Nazeri, 2012), citrus waste (Yang et al., 2013), wheat straw and wood hydrolysate (Kuo & Lee, 2009; Xiang Guo et al., 2013), vinasse (Wu & Liu, 2012), cotton fabric hydrolysate (Kuo et al., 2010), coconut water (Tanskul et al., 2013), etc. Organic nitrogen sources, especially corn steep liquor, showed excellent increase of the yield (Jung et al., 2010; Matsuoka et al., 2014; Nguyen et al., 2008). In order to further increase the production, some additional additives including ethanol, acetic acid, lignosulfonate, sodium alginate, lactate, water-soluble polysaccharides, succinate, Ca^{2+}, and tea were supplemented into media (Thakur, 2014). These additives regulate cellulose synthesis by directly participating in the glycolysis or TCA cycle pathway or adjusting the properties of media (Bae & Shoda, 2005; Lu et al., 2011).

Currently, the bacterial cellulose production is primarily achieved through static fermentation, dynamic fermentation, and cell-free culture. Among them, static fermentation, the process of cellulose film production under static conditions, is still the main traditional fermentation way to produce bacterial cellulose. While, the lower dissolved oxygen, longer cultivation time, and larger cultivation facilities limited the development of the mode. Though dynamic fermentation can improve the dissolved oxygen by shaking or stirring compared with static fermentation, the cells are prone to mutation during mechanical stirring culture, which makes them lose the ability to produce bacterial cellulose. Therefore, cell-free culture, the synthesis without living cells, shows broad development prospects. A cell-free culture system from *Gluconacetobacter hansenii* PJK containing enzyme systems ATP and NADH can use glucose to synthesize the cellulose *in vitro*, and its cellulose yield and glucose conversion efficiency are significantly higher than cells (Ullah et al., 2015). Cell-free culture could reduce the cost of synthetic processes, decrease the metabolic inhibitors, maximize the progress of enzymatic reactions, significantly improve the efficiency and specificity of biochemical reactions, and expand the application scope of biochemical processes (Ullah et al., 2016b).

Overall, bacterial nanocellulose is a natural renewable and sustainable biopolymer which has currently received considerable attention. To improve nanocellulose production, much work will need to be done to explore more novel and efficient cellulose-producing microbial strains. More information on cellulose-producing species would help us to dig deeper into the synthesis process. Moreover, metabolic engineering and process engineering will further optimize cellulose synthesis for industrial applications. Thus, much effort will be paid to optimize the cellulose yield, reduce production costs, and simultaneously expand the scope of applications. It could be expected that the biotechnological process of bacterial cellulose would present further development with the exploration of new species.

Author Contributions

GHL and YD conceived and designed the article. LW performed the literature search and data analysis. GHL and LW wrote the manuscript. YD and QFW critically revised the article. All authors read and approved the manuscript.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability

Experimental data are provided in the manuscript. Authors agree to provide any other data if requested.

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