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The Cell Wall Polysaccharides Biosynthesis in Seaweeds: A Molecular Perspective

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Cell wall polysaccharides (CWPS) of seaweeds play crucial roles in mechanical shear resistance, cell-cell adhesion and the interactions with changeable marine environments. They have diverse applications in food, cosmetics, agriculture, pharmaceuticals and therapeutics. The recent boost of multi-omics sequence analysis has rapidly progressed the mining of presumed genes encoding enzymes involved in CWPS biosynthesis pathways. In this review, we summarize the biosynthetic pathways of alginate, fucoidan, agar, carrageenan and ulvan in seaweeds referred to the literatures on published genomes and biochemical characterization of encoded enzymes. Some transcriptomic data were briefly reported to discuss the correlation between gene expression levels and CWPS contents. Mannuronan C-5 epimerase (MC5E) and carbohydrate sulfotransferase (CST) are crucial enzymes for alginate and sulfated CWPS, respectively. Nonetheless, most CWPS-relevant genes were merely investigated by gene mining and phylogenetic analysis. We offer an integrative view of CWPS biosynthesis from a molecular perspective and discuss about the underlying regulation mechanism. However, a clear understanding of the relationship between chemical structure and bioactivities of CWPS is limited, and reverse genetic manipulation and effective gene editing tools need to be developed in future.

Keywords: cell wall polysaccharide, gene mining, mannuronan C-5 epimerase, carbohydrate sulfotransferase, biosynthesis

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INTRODUCTION

Seaweeds (macroalgae) cover a wide group of algal phyla, and so far about 72,500 known species exist in diversified habitats (Guiry, 2012). Seaweeds, a potential climate change solution, have very important ecological roles in the ocean, serving as the base of the marine food chain and the vital force of marine carbon fixation and sequestration (Campbell et al., 2019; Ortega et al., 2019; Yong et al., 2022). Seaweeds contribute nearly 30% of the world aquaculture production (Cai et al., 2021).

So far, the annual production of world aquatic algae increased over 60 times from 0.56 million tons in 1950 to 35.82 million tons in 2019, with 99.84% from seaweeds and 97% contributed by cultivation (FAO, 2021). The value of the commercial seaweed market worldwide in 2028 was estimated to exceed 24.9 billion U.S. dollars (Shahbandeh, 2021). Seaweeds produce unsaturated fatty acids, minerals, vitamins, phycobiliproteins and polysaccharides for diverse applications in food, animal feed, cosmetics and pharmaceuticals (Vincent et al., 2020). These make seaweeds attract increasing interests in science and industry (Leandro et al., 2020).

Seaweeds are traditionally grouped into three distinct classes based on pigmentation: brown (Ochrophyta), green (Chlorophyta) and red (Rhodophyta) algae (Guiry and Guiry, 2014). They can produce unique carbohydrates due to the complexity of their evolutionary history and habitats (Baldauf, 2008; Coelho and Cock, 2020). The average content of polysaccharides in seaweeds is around 50% (dry weight) and can reach up to 76% (Rioux and Turgeon, 2015). In most taxa of seaweeds, cell walls consist of microfibrillar networks embedded in matrices of diverse polysaccharides and proteins (Domozych, 2016). Cell wall polysaccharides (CWPS) contribute significantly to mechanical shear resistance, cell-cell adhesion, reproduction and morphogenesis, enhanced flexibility and interactions with changeable marine environments. The environmental benefits, ecosystem services and health contributions of seaweeds are inseparable from the biosynthesis of CWPS. Generally, CWPS constitute the largest source of annual renewable biomass on Earth (Domozych, 2016). Specifically, these polysaccharides designate as alginate and fucoidan in brown, agar and carrageenan in red and ulvan in green seaweeds. As macromolecule materials, the structure of these polysaccharides relies on the seaweed species, growth seasons, harvest locations and maturity and so forth. Previously, the extraction, structural determination, activity and function were extensively investigated (Kidgell et al., 2019; Rhein-Knudsen and Meyer, 2021). However, the enzyme-catalyzed biosynthesis of CWPS remains unclear, especially at the molecular level. This actually affects the investigation of the relationships between the structure and function. Clarifying the function of CWPS-related genes will enrich our knowledge on high-value enzymes for their artificial synthesis and optimization *in vitro*. In this review, we summarize the biosynthesis pathways of cell wall polysaccharides in seaweeds and provide a better understanding of their regulatory mechanism.

ALGINATE

In brown seaweeds, cellulose only accounts for 1–8% of total dry weight of the brown seaweeds, whereas the anionic polysaccharides, namely alginate and fucoidan are the main cell wall components (Cronshaw et al., 1958; Kloareg and Quatrano, 1988). Alginate and fucoidan are predominantly extracted from the brown seaweeds (Moradali et al., 2018). Alginate is one linear polysaccharide composed of β-(1-4)-linked D-mannuronic acid (M) and α-L-guluronic acid (G). The M/G ratio and the block composition affect properties of alginate, thus providing either rigidity or flexibility to different tissues of the kelp. The initial investigation of enzymes involved in alginate biosynthesis was focused on mannuronan C-5 epimerase (MC5E), which is responsible for the conversion of M into G residues at the polymer level (Haug and Larsen, 1969). Rødde et al. (1993) measured MC5E activity in *Laminaria digitata*, and found that the synthesis of MC5E in the kelp protoplasts was essential for the new cell wall formation. Nyvall et al. (2003) summarized the pathway of alginate biosynthesis in brown algae, based on the biochemical analysis of the first five steps in *Fucus gardneri* and the cloning of six MC5E full-length coding sequences from *L. digitata*. Within expressed sequence tags (ESTs) dataset, 22 different MC5Es were identified from the cell wall biosynthesis genes (Roeder et al., 2005). The upregulation of MC5E transcripts during protoplast regeneration and sporophyte elicitation enabled *L. digitata* to rapidly modify its cell wall in response to marine environmental variations (Tonon et al., 2008).

So far, seven brown seaweed species had complete or draft genome sequences released, including *Ectocarpus siliculosus* (Cock et al., 2010; Cormier et al., 2017), *Saccharina japonica* (Ye et al., 2015), *Cladosiphon okamuranus* (Nishitsuji et al., 2016, 2020), *Nemacystus decipiens* (Nishitsuji et al., 2019), *Macrocystis pyrifera* (NCBI Bioproject: PRJNA605694), *Sargassum fusiforme* (Wang et al., 2020), and *Undaria pinnatifida* (Shan et al., 2020; Graf et al., 2021). The alginate- and fucoidan-relevant genes in these genomes are listed in **Supplementary Table 1**. The alginate-specific steps in *Ectocarpus* were proposed to be acquired by horizontal gene transfer (HGT) from an actinobacterium (Michel et al., 2010). Chi et al. (2018) found that the rise of the alginate pathway had complex endosymbiotic gene transfer (EGT) origins. Except for providing insights into the origin and evolution of alginate-related genes, these genomic datasets have also enabled the deeper understanding of the regulatory mechanism of alginate biosynthesis. Fischl et al. (2016) generated the first recombinant and active MC5E from brown algae. Subsequently, two soluble MC5Es from *S. japonica* have been proven active in the conversion of M into G (Inoue et al., 2016; Zhang et al., 2021). Tenhaken et al. (2011) isolated a candidate GDP-mannose dehydrogenase (GMD) in the *E. siliculosus* genome and found that Na_2SO_4, NaCl and KCl led to an increase in enzymatic activity. In *S. japonica*, Mg^{2+} could activate two SjGMDs potentially by improving the binding of substrate (Zhang et al., 2016). Subsequently, Zhang et al. (2018) found that the maximum activity of phosphomannomutase/phosphoglucomutase (PMM/PGM) occurred with the presence of Mg^{2+}. Chi et al. (2018) reported that divalent ions of Mg^{2+}, Mn^{2+}, Ca^{2+}, and Cu^{2+} promoted the activity of mannose-1-phosphate guanylyltransferase (MPG). Moreover, the transcriptomic and metabolic analysis revealed that higher expression of alginate biosynthetic genes in *Saccharina* sporophytes might be important for the increased thallus strength and toughness (Chi et al., 2018). Shao et al. (2019) identified candidate genes responsible for the high content of alginate in the distal blade of *S. japonica*.

FUCOIDAN

Fucoidan is a sulfated polysaccharide containing α-(1→3) or α-(1→4)-linked L-fucose, which mainly exists in the cell wall matrix of brown algae and is not found in land plants. In Laminariales species, the concentration and structure of fucoidans vary with reproduction, tissue position, season and environmental factors (Bruhn et al., 2017). The maximum amount of fucoidan was accumulated during reproduction season in *S. japonica*, *Sargassum pallidum*, and *Stephanocystis crassipes*, but was not highly correlated with sea water temperature, salinity and biogenic elements (Skriptsova, 2016). The sulfation and molecular weight of fucoidan influenced its biological activity (Puri et al., 2022). Due to its anticoagulant, antimutagenic, immunostimulatory and antioxidant properties, the fucoidan is predominantly used in pharmaceuticals and therapeutics (Patel, 2012; Puri et al., 2022). Michel et al. (2010) first reported the fucoidan biosynthesis pathway in *E. siliculosus*, and proposed the *de novo* pathway catalyzed by GDP-mannose 4,6-dehydratase (GM46D) and GDP-fucose synthetase (GFS), and the salvage pathway with the involvement of fucokinase (FK) and GDP-fucose pyrophosphorylase (GFPP). Ye et al. (2015) compared the carbohydrate metabolism pathways based on *S. japonica* and 14 other algal genomes, and found that brown algae and diatoms harbor the complete fucoidan biosynthesis pathway. Unlike *E. siliculosus*, one fused FK-GFPP gene encoding a bifunctional enzyme possessing both L-fucokinase and GDP-fucose pyrophosphorylase activities was identified in the genomes of *C. okamuranus* and *N. decipiens* (Nishitsuji et al., 2016, 2019). **Supplementary Table 1** lists the comparison of fucoidan pathway in distinct brown algal genomes. In addition, twenty-seven UDP-D-xylose: L-fucose-α-1,3-D-xylosyltransferases (FucXylTs) specifically catalyzed D-xylose to fucose were identified in brown algae (Han et al., 2019). Lu et al. (2020) screened 104 fucoidan-relevant genes from *S. japonica* and investigated the structure and transcriptional profiles in response to abiotic stress for sulfotransferase (ST) genes. However, the function of ST remains unclear ascribing to the absence of biochemical verification of this enzyme.

AGAR

The hydrocolloids galactan agar is a water-soluble, gel-forming CWPS in red seaweeds and is widely used in food, pharmaceutical and biotechnology fields. The major agarophytes are *Gracilaria*, *Curdiea*, *Hydropuntia*, *Gelidium*, and *Pterocladia* (Sasuga et al., 2017). The agar biosynthesis was poorly understood and the hypothetical pathway was mainly deduced from chemical analysis in land plants and red seaweeds (Collén et al., 2004). Lee et al. (2017) proposed an agar biosynthetic pathway that starts from fructose-6-phosphate (F6P), which is then catalyzed to UDP-D-galactose (by galactose-1-phosphate uridylyltransferase, GALT) and GDP-L-galactose (by GDP-mannose-3,5-epimerase, GME) to form agar precursor chain. **Figure 1** shows the schematic diagram of agar biosynthesis. Prior to this hypothetical pathway, GALT and GME were individually verified to have a regulatory role on the content of agar. The cloning and structure analysis of *GALT* has been reported in *Gracilaria gracilis* (Lluisma and Ragan, 1998) and *Gracilariopsis lemaneiformis* (Li et al., 2010). The *GALT* and *GME* transcripts and enzyme activities were found to be highest in *G. changii* and lowest in *G. salicornia*, corresponding to their respective agar yields (Siow et al., 2012, 2013). The relationship between agar content and expression levels of UDP-glucose pyrophosphorylase (UGP) gene in *G. lemaneiformis* indicated that UGP was a potential molecular marker to reflect the agar yields (Chang et al., 2014). Recently, Yu et al. (2021) identified one *GALT* gene from *Neoporphyra haitanensis*, and proposed that it might be derived from primary endosymbiotic eukaryotic hosts. Unlike GALT, GME and UGP, which are shared by many organisms, the galactosyl transferases were unique in agarophytes and were difficult to be identified. The *G. changii* genome annotated homologous genes for chondroitin sulfate synthases and chondroitin sulfate *N*-acetylgalactosaminyl transferase, which were regarded as potential galactosyl transferases for agar biosynthesis in *Gracilaria* (Ho et al., 2018). In addition, two carbohydrate sulfotransferase (CST) genes belonging to the sulfotransferase subfamily 2 were believed to be candidate genes for agar sulfotransferases (Ho et al., 2018). Nonetheless, the function of these presumed genes in *Gracilaria* awaits further investigation.

CARRAGEENAN

Carrageenans are commercially extracted from *Kappaphycus* and *Eucheuma*, and are dominantly produced in Indonesia, the Philippines and Malaysia (Porse and Rudolph, 2017). Usually, carrageenan can be used as additives in food, beverage, agriculture and animal feed and so forth. Molecular study on carrageenan biosynthesis remains very limited. To date, the only biochemically characterized enzymes in this pathway are galactose sulfurylases (Genicot-Joncour et al., 2009; Lipinska et al., 2020). Within the *Chondrus* genome dataset, genes encoding carrageenan-relevant enzymes, including CST, glycosyltransferase (GT), glycoside hydrolase (GH16), and galactose-6-sulfurylase were identified (Collén et al., 2013, 2014). CSTs and GTs in carrageenan biosynthesis in *C. crispus* were closely related to those involved in the synthesis of sulfated animal sugars, implying an ancient eukaryotic origin for these pathways (Ficko-Blean et al., 2015). The findings of conserved CSTs in brown seaweeds and red seaweeds through convergent evolution, which were not found in land plants and freshwater algae, inferred a critical role of sulfated polysaccharides in adapting to high-salinity environment (Brawley et al., 2017). The differential gene expression of carrageenan-related genes in carrageenanophytes were reported. Song et al. (2014) identified 8 differentially expressed KEGG orthologs for sulfur metabolism which might be related to the biosynthesis of three types of carrageenans in *Betaphycus*, *Kappaphycus*, and *Eucheuma*. Differential expression of multigenic genes of *CSTs*, *GTs*, *GH* and galactose-sulfurylases supported that carrageenan biosynthesis played a crucial role in the physiological

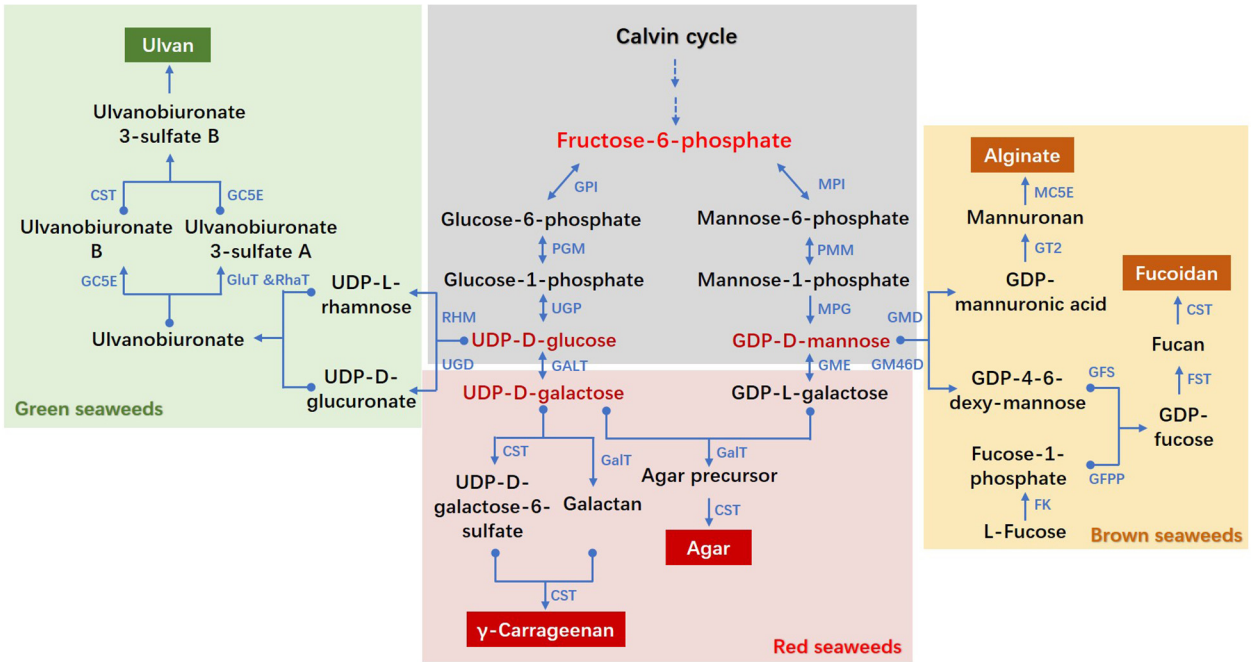

FIGURE 1 | Proposed biosynthesis pathways of cell wall polysaccharides in seaweeds. CST, carbohydrate sulfotransferase; FK, fucokinase; FST, fucosyltransferase; GalT, galactosyltransferase; GALT, galactose-1-phosphate uridylyltransferase; GC5E, glucuronyl C5-epimerase; GFS, GDP-fucose synthetase; GFPP, GDP-fucose pyrophosphorylase; GluT, glucuronyltransferase; GM46D, GDP-mannose 4,6-dehydrogenase; GMD, GDP-mannose dehydrogenase; GME, GDP-mannose-3′,5′-epimerase; GPI, glucose-6-phosphate isomerase; GT, glycosyltransferase; MC5E, mannuronate C5-epimerase; MPI, mannose-6-phosphate isomerase; MPG, mannose-1-phosphate guanylyltransferase; PGM, phosphoglucomutase; PMM, phosphomannomutase; RhaT, α-1,4-rhamnosyltransferase; RHM, rhamnose synthase; UGD, UDP-D-glucose dehydrogenase; UGP, UTP-glucose-1-phosphate uridylyltransferase. The pathways referred to diverse literatures: (Lahaye and Robic, 2007; Collén et al., 2014; Ficko-Blean et al., 2015; Lee et al., 2017; Chi et al., 2018; Ho et al., 2018; Shao et al., 2019; Lipinska et al., 2020).

differentiation between the isomorphic life cycle stages of *C. crispus* (Lipinska et al., 2020).

ULVAN

The CWPS in Ulvaceae species account for 38–54% of cell dry weight with a majority of water-soluble ulvan (Lahaye and Kaeffer, 1997). In green seaweeds, the genera *Ulva*, *Monostroma*, and *Gayralia* synthesize the highly anionic ulvan polysaccharides (Domozych et al., 2012). As a gelling sulfated polysaccharide, ulvan attracts significant interest in the fields of agriculture, human health, and biomaterials. It is a complex polyanionic heteropolysaccharide with sugar compositions of rhamnose, glucuronate, iduronate and xylose (Kidgell et al., 2019). Lahaye and Robic (2007) proposed pathways for the biosynthesis of these four nucleotide sugar precursors of ulvan. On this basis, an enzyme-catalyzed ulvan biosynthesis pathway was proposed but none of the enzyme activities were experimentally verified (Ficko-Blean et al., 2015). Sea lettuce genome released potential genes encoding cell wall-related protein, but the polysaccharide biosynthesis was not discussed (De Clerck et al., 2018). Although no CST homologs were found in *Chara* genome, these genes conserved with those in animals, brown seaweeds and red seaweeds were retrieved from *Ulva* genome (Nishiyama et al., 2018; Kloareg et al., 2021). Phylogenetic analysis revealed that these CSTs were lost in freshwater and land plants, which solidly supported the hypothesis that cell wall sulfated polysaccharides were lost in the green lineage as an adaption to sulfate-scarce freshwater and terrestrial environments (Kloareg et al., 2021). Based on the above research, **Figure 1** displayed the presumed ulvan biosynthesis pathway, with a disaccharide unit of rhamnose and iduronate.

CONCLUSION AND PERSPECTIVES

The activity and function of CWPS depend on their structure composition, and the latter is affected by catalytic enzymes at each step of the metabolic pathway. In this review, we have summarized the molecular evidence supporting the presence of genes encoding enzymes responsible for the biosynthesis of alginate, fucoidan, agar, carrageenan and ulvan. Together with the previously proposed pathways of CWPS metabolism in seaweeds, which were predominantly deduced from *in vivo* enzyme isolation and chemistry analysis, we constructed a schematic diagram of cell wall polysaccharide biosynthesis pathways with F6P as a common upstream metabolite (**Figure 1**). There are three important intermediate metabolites, GDP-D-mannose, UDP-D-glucose and UDP-D-galactose. GDP-D-mannose is the last shared metabolite for alginate, fucoidan and agar/carrageenan, whereas UDP-D-glucose is a common

upstream metabolite for ulvan and agar/carrageenan. From UDP-D-galactose, agar or carrageenan is individually synthesized in different red algal species. The corresponding branching enzymes of GMD, GM46D, GME, UGD, and GALT therefore play important roles in the synthesis of specific CWPS in each seaweed. Fucoidan, agar, carrageenan and ulvan are sulfated polysaccharides, of which CSTs are key enzymes for their structure composition. In the last decade, the mining of CWPS-related genes has rapidly progressed ascribing to the completion of a series of multicellular algal genomes. Gene origin and evolution through phylogenetic analysis was the research focus, with a few genes' heterologous expression and recombinant enzyme kinetic analysis. However, functional verification of corresponding genes was lagging due to the lack of reverse genetic manipulation and effective gene editing tools in macroalgae. Intensive study and functional verification of CWPS genes are highly needed to further clarify their biosynthesis pathways in seaweeds.

AUTHOR CONTRIBUTIONS

ZS and DD conceptualized the manuscript. ZS wrote the draft manuscript. DD reviewed and revised the manuscript. Both authors approved the final submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpls.2022.902823/full#supplementary-material

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