

Invited Review

Carotenogenesis in cyanobacteria: CruA/CruP-type and CrtL-type lycopene cyclases

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Cyanobacteria are oxygenic photoautotrophic prokaryotes containing chlorophylls and carotenoids, and the latter play important roles in light-harvesting, protection of excess light, assembly of pigment-protein complexes, and stabilization of lipid membranes. Cyanobacteria produce many kinds of carotenoids, such as β -carotene, zeaxanthin, echinenone, and myxol glycosides, which have a cyclic structure at one or both end(s). Cyclization of lycopene is a branch point in carotenoid biosynthesis to β -carotene and γ -carotene. Two types of lycopene cyclases, CruA/CruP-type and CrtL-type, are functionally confirmed in only five species, while homologous genes are found in the genomes of most cyanobacteria. This review summarizes the carotenogenesis pathways and the functional enzymes along with genes, focusing particularly on the cyclization of lycopene by distinct types of lycopene cyclases in cyanobacteria.

Key Words: carotenoid; CrtL; CruA; CruP; cyanobacteria; lycopene cyclase

Introduction

Carotenoids are synthesized in all phototrophic organisms and many non-phototrophic organisms, including bacteria, archaea, algae, fungi, and land plants. In phototrophic organisms, they play important roles in light-harvesting, protection of excess light, assembly of pigment-protein complexes, and stabilization of lipid membranes (Takaichi, 2011, 2013).

Cyanobacteria are considered to originate from photo-

synthetic bacteria, and to have given rise to plant chloroplasts through evolution and symbiosis. The carotenoid structures and carotenogenesis pathways differ among photosynthetic bacteria, cyanobacteria, and chloroplasts, and, accordingly, carotenoids seem to change continuously. It is interesting to speculate on how these different carotenogenesis pathways have evolved and been obtained. Cyanobacteria can synthesize a variety of carotenoids. Most ordinary cyanobacteria contain β -carotene and its derivatives such as zeaxanthin, echinenone, and nostoxanthin; and also unique carotenoid glycosides, such as myxol fucoside and ketomyxol chinovoside (Takaichi and Mochimaru, 2007). These carotenoids are cyclized at one or both ends of the structure. This cyclization reaction is catalyzed by lycopene cyclase. Thus far, several types of lycopene cyclases have been confirmed in various organisms including cyanobacteria (Sugiyama et al., 2017; Takaichi, 2013; Xiong et al., 2017). Furthermore, this is the branching point of β -carotene and γ -carotene: from β -carotene, echinenone, zeaxanthin and nostoxanthin are produced; and from γ -carotene, myxol glycoside, ketomyxol glycoside and 2-hydroxymyxol glycoside are produced (Takaichi and Mochimaru, 2007). In this review, we summarize the carotenogenesis pathway, the functional enzymes as well as genes in cyanobacteria. We particularly focus on the cyclization of lycopene by distinct types of lycopene cyclases.

Carotenoid biosynthesis in cyanobacteria

The entire nucleotide sequence of the cyanobacteria genome was first elucidated in *Synechocystis* sp. PCC 6803 (Kaneko et al., 1996). Since then, the identification of carotenoids, including the chirality of hydroxyl groups and the determination of glycoside, and the genes involved in carotenogenesis, have been reported (Takaichi et al., 2001,

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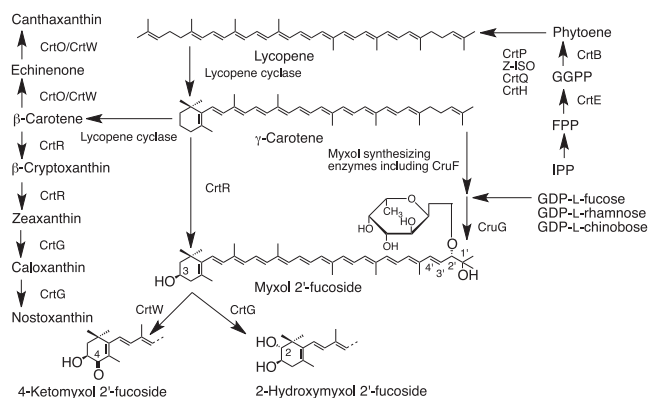


Fig. 1. Main pathways of carotenogenesis and enzymes in cyanobacteria.

CrtE, geranylgeranyl diphosphate synthase; CrtB, phytoene synthase; CrtP, phytoene desaturase; Z-ISO, ζ -carotene isomerase; CrtQ, ζ -carotene desaturase; CrtH, *cis*-carotene isomerase; CrtR, β -carotene hydroxylase; CrtO, β -carotene ketolase; CrtW, β -carotene ketolase; CrtG, 2,2'- β -hydroxylase; CruF, C-1'-hydratase; CruG, 2'-*O*-glycosyltransferase; IPP, isopentenyl diphosphate; FPP, farnesyl diphosphate; GGPP, geranylgeranyl diphosphate.

2005).

Based on the identification of the chemical structures of carotenoids and the genes involved in carotenogenesis in cyanobacteria, the carotenoid biosynthesis pathways are summarized in Fig. 1. Geranylgeranyl diphosphate (GGPP) is produced from farnesyl diphosphate and isopentenyl phosphate catalyzed by GGPP synthase (CrtE), and then two molecules of GGPP are condensed to the first C40 carotenoid, phytoene, catalyzed by phytoene synthase (CrtB). CrtE from *Thermosynechococcus elongatus* (Ohto et al., 1999) and CrtB from *Synechococcus* sp. PCC 7942 (Chamovitz et al., 1992), *Synechocystis* sp. PCC 6803 (Martínez-Férez et al., 1994) and *Gloeobacter violaceus* (Steiger et al., 2005), are functionally confirmed. These reactions are common in all carotenogenic organisms. Phytoene is converted to lycopene via a series of desaturation and isomerization events. Cyanobacteria, as well as land plants, need four enzymes; phytoene desaturase (CrtP), ζ -carotene desaturase (CrtQ), ζ -carotene isomerase (Z-ISO), and *cis*-carotene isomerase (CrtH). Exceptionally, the primitive cyanobacterium *Gloeobacter violaceus* PCC 7421, uses only one enzyme of bacterial-type phytoene desaturase (CrtI) to convert phytoene to lycopene (Steiger et al., 2005; Tsuchiya et al., 2005). CrtP from *Synechocystis* sp. PCC 6803 (Bautista et al., 2005), *Anabaena* sp. PCC 7120 (Breitenbach et al., 2013) and *Synechococcus* sp. PCC 7942 (Chamovitz et al., 1992) and CrtQ from *Synechocystis* sp. PCC 6803 (Bautista et al., 2005) and *Anabaena* sp. PCC 7120 (Breitenbach et al., 2013) are functionally confirmed. Z-ISO from *Arthrospira platensis* NIES-39, which converts 9,15,9'-*tri-cis* ζ -carotene to 9,9'-*di-cis* ζ -carotene, has been functionally identified very recently (Sugiyama et al., 2020). CrtH converts poly-*cis* neurosporene and lycopene to all-*trans* neurosporene and lycopene, respectively (Breitenbach et al., 2001; Masamoto et al., 2001). Furthermore, these functions of two isomerases can be replaced by light during cultivation.

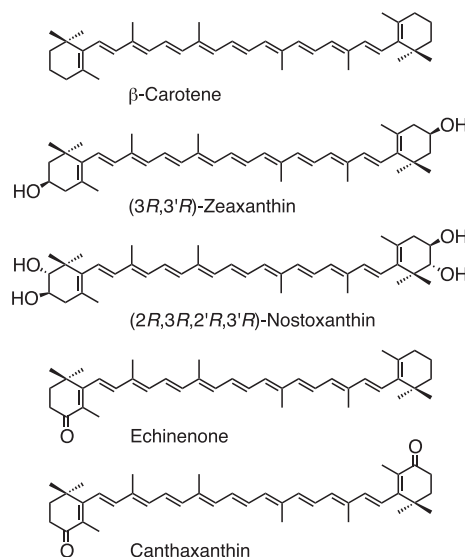


Fig. 2. Structure of some carotenoids found in cyanobacteria.

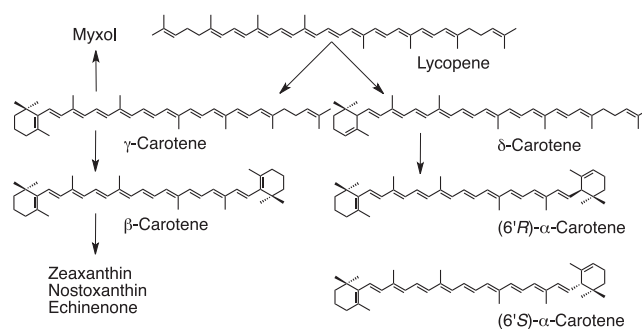


Fig. 3. Reaction of lycopene cyclases.

α -Carotene is found in only two genera of cyanobacteria.

Lycopene is cyclized to β -carotene via γ -carotene by lycopene cyclase as described below. Zeaxanthin is synthesized from β -carotene by β -carotene hydroxylase (CrtR), and then nostoxanthin is produced from zeaxanthin by 2,2'- β -hydroxylase (CrtG). CrtR from *Synechocystis* sp. PCC 6803 (Masamoto et al., 1998) and *Anabaena* sp. PCC 7120 (Mochimaru et al., 2008) are functionally confirmed. The CrtG in some cyanobacteria, such as *Thermosynechococcus elongatus*, also catalyzes the conversion of both myxol 2'-fucoside to 2-hydroxymyxol 2'-fucoside and zeaxanthin to nostoxanthin (Iwai et al., 2008). Consequently, CrtG in cyanobacteria is used in two pathways, and, furthermore, these two hydroxylases do not have sequence homologies.

Two distinct β -carotene ketolases, CrtO and CrtW, are distributed in cyanobacteria, and they do not have sequence homologies (Takaichi, 2011). In *Anabaena* sp. PCC 7120, CrtO catalyzes the conversion of β -carotene into echinenone, while CrtW catalyzes the conversion of myxol 2'-fucoside into 4-ketomyxol 2'-fucoside (Mochimaru et al., 2005). *Nostoc punctiforme* PCC 73102 has two versions of CrtW; one produces echinenone, and the other produces 4-ketomyxol 2'-fucoside (Steiger and Sandmann, 2004). Some other versions of CrtO and CrtW are functionally confirmed in some cyanobacteria (Takaichi, 2011).

Table 1. Functionally confirmed CruA and candidates of CruA in cyanobacteria. The query sequence is for functional CruA from *Synechococcus* sp. PCC 7002.

Species	Query sequence for BLAST: ACB00134.1 from <i>Synechococcus</i> sp. PCC 7002 ^a		
	Accession No.	Length of amino acid	Identities(%)E-value
<i>Acaryochloris marina</i> MBIC11017	ABW30381.1	678	63/0.0
<i>Anabaena cylindrica</i> PCC 7122	AFZ55937.1	694	65/0.0
<i>Arthrospira platensis</i> NIES-39 ^b	BAI88473.1	648	65/0.0
<i>Calothrix</i> sp. PCC 6303	AFZ00523.1	693	63/0.0
<i>Chroococcidiopsis thermalis</i> PCC 7203	AFY90645.1	711	63/0.0
<i>Cyanobacterium stanieri</i> PCC 7202	AFZ47372.1	663	62/0.0
<i>Gloeobacter kilaueensis</i> JS1	AGY59763.1	668	56/0.0
<i>Gloeobacter violaceus</i> PCC 7421	BAC91539.1	669	57/0.0
<i>Gloeocapsa</i> sp. PCC 7428	AFZ30695.1	700	65/0.0
<i>Nostoc</i> sp. PCC 7524	AFY50143.1	707	65/0.0
<i>Pseudanabaena</i> sp. PCC 7367	AFY68915.1	682	61/0.0
<i>Stanieria cyanosphaera</i> PCC 7437	AFZ37407.1	667	67/0.0
<i>Synechocystis</i> sp. PCC 6803 ^c	AGF52244.1	668	64/0.0
<i>Thermosynechococcus elongatus</i> BP-1	BAC08691.1	681	61/0.0
<i>Trichodesmium erythraeum</i> IMS101	ABG51022.1	680	64/0.0
<i>Xenococcus</i> sp. PCC 7305	ELS02858.1	674	66/0.0

^{a,b,c}Functionally confirmed CruA (Maresca et al., 2007; Sugiyama et al., 2017; Xiong et al., 2017), respectively.

Table 2. Functionally confirmed CruP and candidates of CruP in cyanobacteria. The query sequence is for functional CruP from *Synechococcus* sp. PCC 7002.

Species	Query sequence for BLAST: ACA98060.1 from <i>Synechococcus</i> sp. PCC 7002*		
	Accession No.	Length of amino acid	Identities(%)E-value
<i>Acaryochloris marina</i> MBIC11017	ABW27396.1	515	51/5E-178
<i>Anabaena cylindrica</i> PCC 7122	AFZ57722.1	513	54/0.0
<i>Arthrospira platensis</i> NIES-39	BAI91715.1	517	53/0.0
<i>Calothrix</i> sp. PCC 6303	AFZ00523.1	515	53/0.0
<i>Chroococcidiopsis thermalis</i> PCC 7203	AFY85651.1	548	53/0.0
<i>Cyanobacterium stanieri</i> PCC 7202	AFZ48421.1	504	56/0.0
<i>Gloeobacter kilaueensis</i> JS1	AGY59595.1	513	52/2E-170
<i>Gloeobacter violaceus</i> PCC 7421	BAC90425.1	514	54/8E-167
<i>Gloeocapsa</i> sp. PCC 7428	AFZ04321.1	518	56/0.0
<i>Nostoc</i> sp. PCC 7524	AFY47984.1	514	56/0.0
<i>Pseudanabaena</i> sp. PCC 7367	AFY70543.1	546	50/4E-179
<i>Stanieria cyanosphaera</i> PCC 7437	AFZ37766.1	516	58/0.0
<i>Synechocystis</i> sp. PCC 6803	AGF53056.1	522	55/0.0
<i>Synechococcus elongatus</i> PCC 7942	ABB56684.1	529	55/2E-156
<i>Trichodesmium erythraeum</i> IMS101	ABG49950.1	517	54/0.0
<i>Xenococcus</i> sp. PCC 7305	ELS03497.1	514	55/0.0

*Functionally confirmed CruP (Maresca et al., 2007).

Table 3. Functionally confirmed CrtL and candidates of CrtL in cyanobacteria. The query sequence is for functional CrtL from *Synechococcus elongatus* PCC 7942.

Species	Query sequence for BLAST: ABB58092.1 from <i>Synechococcus elongatus</i> PCC 7942 ^a		
	Accession No.	Length of amino acid	Identities(%)E-value
<i>Acaryochloris marina</i> MBIC11017	ABW31007.1	411	59/1E-180
<i>Prochlorococcus marinus</i> MED4 ^b	CAE19092.1	427	50/1E-152
<i>Prochlorococcus marinus</i> MED4 ^b	CAE19523.1	403	51/6E-151

^{a,b}Functionally confirmed CrtL (Cunningham et al., 1994; Stickforth et al., 2003), respectively.

In conclusion, echinenone and canthaxanthin may be produced by CrtO and/or CrtW, and 4-ketomyxol and astaxanthin may be produced by CrtW depending on the species (Takaichi, 2013).

Myxol is presumably synthesized from monocyclic γ -carotene. The left half (β end group) of the γ -carotene is hydroxylated by CrtR, and then a keto group and a 2'-hydroxy group are introduced by CrtW and CrtG, respec-

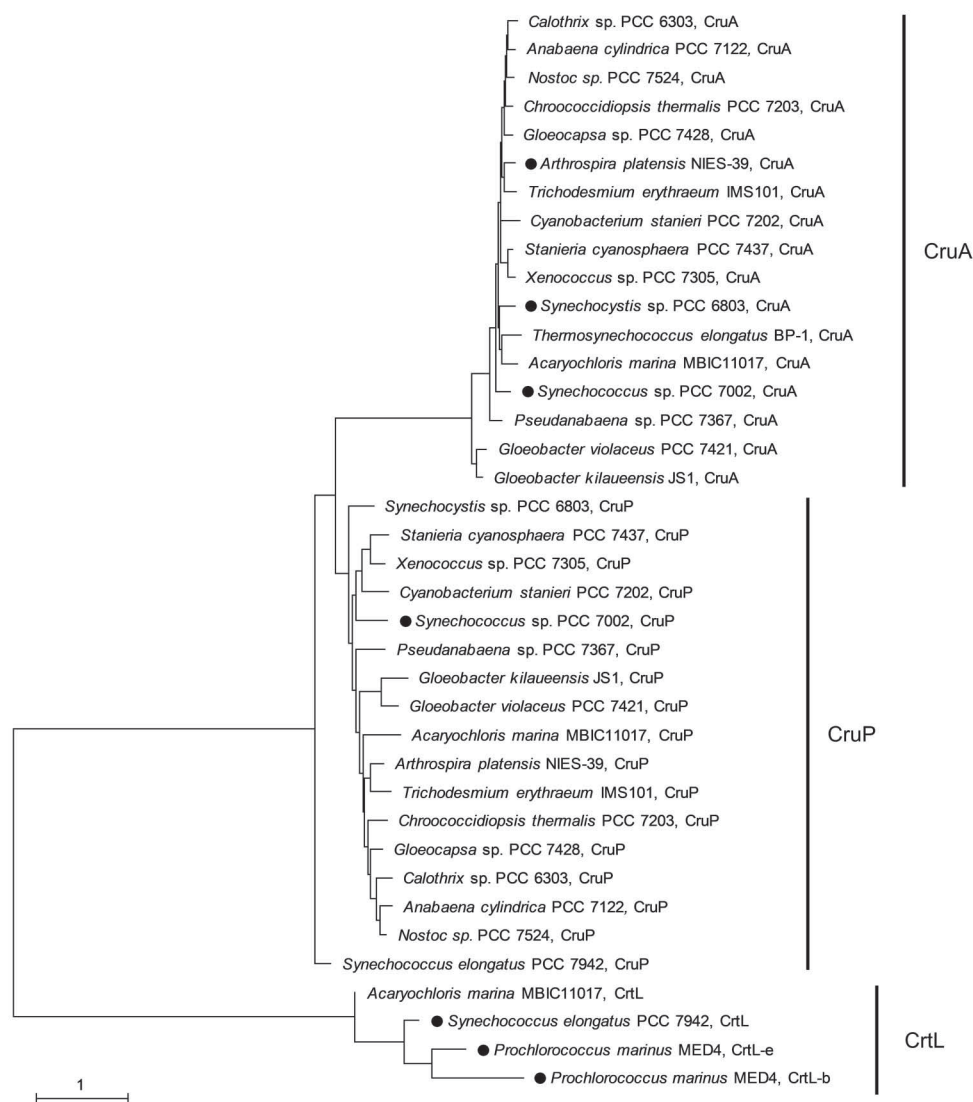


Fig. 4. Phylogenetic tree generated based on deduced amino acid sequences of CruA/CruP-type and CrtL-type lycopene cyclase from cyanobacteria.

The tree was constructed using the Neighbor-Joining method using bootstrapping (1,000 replicates). Accession numbers of protein sequences are given in Tables 1, 2, and 3. The functional CruA-, CruP-, and CrtL-type lycopene cyclases are represented by black circles on the left.

tively (Fig. 1). Most cyanobacteria contain unique myxol glycosides, and the glycoside moieties are usually methylpentose; fucose, rhamnose, and chinovose (Takaichi, 2011, 2013). Some enzymes such as C-1'-hydroxylase (CruF) and 2'-O-glycosyltransferase (CruG) are reported to be involved in myxol glycoside synthesis (Graham and Bryant, 2009). However, little is known about these processes. Further studies of the enzymes and genes involved in the biosynthesis of myxol glycosides are required.

Lycopene cyclase

The cyclization of lycopene is a branch point in carotenoid biosynthesis pathways; β -carotene, γ -carotene to myxol, and α -carotene. Lycopene is cyclized into either β -carotene via γ -carotene by lycopene β -cyclase, or α -carotene via δ -carotene by lycopene ε -cyclase (Fig. 3). Lycopene cyclases can be divided into three types based on the amino acid sequences. These lycopene cyclases have

been functionally confirmed in some carotenogenic organisms (Maresca et al., 2007; Takaichi, 2011).

The first type of lycopene cyclase is CrtY in bacteria and CrtL (CrtL-b, Lcy-b) in cyanobacteria, algae, and plants, which has an NAD(P)/FAD-binding motif. Lycopene ε -cyclases (CrtL-e, Lcy-e) in cyanobacteria and plants, and lycopene β -monocyclases (CrtYm, CrtLm) in bacteria are also included in this type. Note that Maresca et al. (2007) divide this type into two CrtY- and CrtL-types.

The second type is a heterodimer (CrtYc and CrtYd) in bacteria, a monomer (CrtYc-Yd) in archaea, and fused and bifunctional CrtYB in fungi, but not found in phototrophs (Hemmi et al., 2003; Takaichi, 2011).

The third type, CruA, was first found in a green sulfur bacterium, *Chlorobaculum tepidum*, and two homologous genes of CruA, *cruA* and *cruP*, are widely distributed among different species of cyanobacteria, as described below (Tables 1 and 2) (Takaichi, 2013).

Lycopene cyclase in cyanobacteria

To date, only seven lycopene cyclases from five species have been functionally confirmed in cyanobacteria (Tables 1–3, Fig. 4).

A gene encoding CrtL-type lycopene cyclase was first isolated from *Synechococcus elongatus* PCC 7942 and characterized by functional complementation analysis in transformed *Escherichia coli*, which produced mainly lycopene (Cunningham et al., 1994). *Prochlorococcus marinus* MED4 contains mainly α -carotene and β -carotene, and two CrtL-type lycopene cyclases, CrtL-b and CrtL-e were functionally identified using lycopene producing *E. coli* (Stickforth et al., 2003). CrtL-b exhibits lycopene β -cyclase activity, whereas CrtL-e is a bifunctional enzyme, having both lycopene ϵ -cyclase and lycopene β -cyclase activities. The combination of these two cyclases enables the production of β -, α -, and ϵ -carotenes.

Acaryochloris marina MBIC11017 synthesizes β -carotene and the unusual (6'S)- α -carotene, which shows opposite chirality to the usual (6'R)- α -carotene, and is the only species to have such a carotene in nature (Fig. 3) (Takaichi et al., 2012). Interestingly, *Acaryochloris marina* MBIC11017 contains the *crtL* homologous gene and the homologous genes of *cruA* and *cruP*, the gene products of which are 63% and 51% amino acid identities for the functional *Synechococcus* sp. PCC 7002 *cruA* and *cruP*, respectively (Tables 1–3). However, there is no information on the function of *crtL*-, *cruA*-, and *cruP*-like gene products in this cyanobacterium. Further studies are needed to elucidate the detail of each functional lycopene cyclase in cyanobacteria.

Two lycopene cyclases, *cruA* and a paralog known as *cruP*, in *Synechococcus* sp. PCC 7002 were shown to have lycopene cyclase activity, by using lycopene producing *E. coli*. Bradbury et al. (2012) reported that they were unable to replicate the cyclase activity of *cruP* in *Synechococcus* sp. PCC 7002 in *E. coli* (Bradbury et al., 2012). Based on the carotenoid profile of the *cruP*-deficient mutants, they proposed that the role of *cruP* should be rather on reducing oxidative damage caused by singlet oxygen. Recently, Sugiyama et al. (2017) have reported that *cruA* in *Arthrospira platensis* NIES-39 has lycopene cyclase activity, whereas *cruP* does not, by using lycopene producing *E. coli*. Furthermore, Xiong et al. (2017) found that *cruA* in *Synechocystis* sp. PCC 6803 has lycopene cyclase activity and requires a bound chlorophyll *a* for activation. *cruA* in *Synechocystis* sp. PCC 6803, expressed in lycopene producing *E. coli* strains, did not produce β -carotene (Xiong et al., 2017), and similar experiments were also performed with determined efforts of various laboratories in the world. However, the expression of *cruA*, isolated from *Synechocystis* sp. PCC 6803, in the *Synechococcus* sp. PCC 7002 *cruA* deletion mutant produced identical carotenoids to the wild type (Xiong et al., 2017). The *cruA* expressed in *Synechocystis* sp. PCC 6803 was purified from *Synechococcus* sp. PCC 7002, and the purified protein contained chlorophyll *a* and β -carotene (Xiong et al., 2017). The function of bound chlorophyll *a* is unknown.

The homologous genes of *cruA* and *cruP* are widely dis-

tributed in the genomes of some cyanobacteria species (Tables 1 and 2); however, there are only a few reports that showed lycopene cyclase activity in these gene products.

Phylogenetic analysis of the functional *cruA*-, *cruP*-, and CrtL-type lycopene cyclases with their homologs in cyanobacteria shows that three individual clusters are formed (Fig. 4). The *cruA*, *cruP*, and CrtL homologs are placed in the same cluster as each functional lycopene cyclase, except for *cruP* homologs in *Synechococcus elongatus* PCC 7942, and the CrtL-type cyclase forms a clade distinct from the *cruA*- and *cruP*-type cyclases.

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