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Genetic control for light-induced carotenoid production in non-phototrophic bacteria

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Abstract Carotenoids are naturally occurring yellow or orange pigments that serve as a protectant against photo-oxidative damages. Among the wide variety of producers, the prokaryotes generate a broad spectrum of carotenoids with diverse chemical structures that are expected to have a high potential in biotechnological applications. Bacterial carotenogenesis occurs in a constitutive or light-induced manner, which suggests the diversity of the regulatory mechanism. The mechanism for light-induced carotenoid production in non-phototrophic bacteria has been studied in detail in *Myxococcus xanthus*, a Gram-negative gliding bacterium. The complicated mechanism involves the activation of an extracytoplasmic function (ECF) sigma factor (CarQ), which leads to the sequestration of a MerR family transcriptional regulator (CarA) that represses the expression of the carotenoid biosynthesis genes in the dark. Recently, we identified another regulatory mechanism for light-induced carotenogenesis in *Streptomyces coelicolor* A3(2), a Gram-positive soil bacterium. In this organism, the transcription of the carotenoid biosynthesis gene cluster is specified by LitS, a photo-inducible ECF sigma factor. The evidence indicates that the photo-dependent transcription of *litS* is mediated by LitR, a MerR family transcriptional regulator. In addition, it is suggested that the conformational alteration of LitR upon receiving the illumination signal determines its binding to DNA. The carboxy-terminal domain of LitR contains a possible binding site for Vitamin B12, which may serve as a capturing apparatus for the illumination signal.

Keywords Carotenoid · Non-phototrophic bacteria · Light-induced transcription · ECF sigma factor · MerR-type regulator

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Introduction

Carotenoids comprise a major class of pigment molecules that occur in all photosynthetic organisms from bacteria to plants as well as in non-phototrophic bacteria and fungi [2]. In both phototrophic and non-phototrophic organisms, these compounds serve as a protectant against photo-oxidative damages by scavenging harmful radicals, which are formed upon illumination. They also serve as a light-capturing apparatus in phototrophic organisms. The biosynthesis genes for carotenoids have been cloned from various organisms, and the enzymes involved in the biosynthesis pathway have been precisely characterized [2, 3]. In this paper, we focus on prokaryotic carotenogenesis and present an overview on the recent research progress with regard to the genetic control mechanism for light-induced carotenoid production in non-phototrophic bacteria.

Carotenogenesis in prokaryotes

Table 1 summarizes the prokaryotic organisms that are known to produce carotenoids. The ability is widely distributed among the organisms including bacteria and archaea. Prokaryotes produce a broad spectrum of carotenoids with diverse chemical structures in comparison to eukaryotes. Some molecular species such as β-carotene and astaxanthin have wide applications in food, pharmaceutical and chemical industries, and certain microbes are effective producers of these compounds.

Carotenogenesis in prokaryotes occurs in a constitutive, light-induced or cryptic manner (Table 1). Whereas the majority of microbes reported produce carotenoids constitutively, some organisms belonging to *Myxococcus*, *Streptomyces*, *Mycobacterium*, *Agromyces* and *Sulfolobus* form these pigments when the cells are illuminated. The two *Streptomyces* spp., *Streptomyces setonii* and *Streptomyces griseus*, are designated as cryptic since the condition for carotenoid production in these organisms is unknown (see below).

Table 1 Prokaryotic carotenoid producers

Organism	Main carotenoids	Light-dependence	Reference
Eubacteria, gram-negative			
Myxococcus spp.	Myxobactin, Myxobacton, 4-Ketotorulene	Light induced	[10, 22]
Rhodobacter capsulatus	Spheroidene, Neurosporene	Constitutive	[1]
Thiocapsa roseopersicina	Spirilloxanthin	Constitutive	[44]
Pantoea agglomerans	Lycopene, β-Carotene, Zeaxanthin	Constitutive	[23]
Erythrobacter longus	β-Carotene, rubixanthan	Constitutive	[48]
Agrobacterium aurantiacum	Astaxanthin, 4-Ketozeaxanthin	Constitutive	[53]
Bradyrhizobium spp.	Canthaxanthin, Spirilloxanthin	Constitutive	[36]
Pseudomonas sp. SD-212	Astaxanthin, 2-Hydroxyastaxanthin	Constitutive	[54]
Paracoccus carotinifaciens	Astaxanthin	Constitutive	[50]
P. marcusii	Astaxanthin	Constitutive	[20]
P. haeundaensis	Astaxanthin	Constitutive	[35]
P. zeaxanthinifaciens	Zeaxanthin	Constitutive	[7, 37]
Paracoccus sp.	Astaxanthin	Constitutive	[53]
Eubacteria, gram-positive			
Streptomyces coelicolor A3(2)	β-Carotene, Isorenieratene	Light induced	[49]
Streptomyces setonii	Not identified	Cryptic	[28]
Streptomyces griseus	β-Carotene, Isorenieratene	Cryptic	[31, 34]
Brevibacterium sp. strain 103	β-Carotene, Astacin, Astaxanthin	Constitutive	[24, 43]
Brevibacterium sp.	β-Carotene, Echinenone, Canthaxanthin	Constitutive	[40]
Mycobacterium marinum	β-Carotene	Light induced	[41]
Micrococcus roseus	Canthaxanthin, Bacterioruberins	Constitutive	[14, 47]
Agromyces mediolanensis	Decaprenoxanthin	Light induced	[51]
Corynebacterium sp.	Decaprenoxanthin	Constitutive	[17]
Corynebacterium glutamicum	Lycopene, Decaprenoxanthin	Constitutive	[30]
Chlorobium limicola	Neurosporene, Lycopene, Chlorobactene	Constitutive	[45]
Synechocystis sp.	Myxoxanthophyll, β-Carotene, Echinenone, Zeaxanthin	Constitutive	[33]
Archaea			
Halobacterium sp.	β-Carotene, Lycopene, Bacterioruberins	Constitutive	[17]
Haloferax volcanii	Bacterioruberins, Lycopene	Constitutive	[42]
Halobacterium salinarium	Astaxanthin, Bacterioruberins	Constitutive	[11]
Haloferax alexandrinus	Canthaxanthin, Bacterioruberins	Constitutive	[4, 5]
Sulfolobus shibatae	Zeaxanthin glycosides	Constitutive	[32]
Sulfolobus solfataricus	Zeaxanthin glycosides	Constitutive	[21]
Sulfolobus spp.	Not identified	Light induced	[19]

The regulatory mechanisms for the light-induced carotenoid production should involve a light-sensing mechanism(s), which couples to the genetic regulation for the expression of carotenoid biosynthesis genes. As described below, the light-dependent transcriptional control for carotenogenesis has been extensively studied in *Myxococcus xanthus*. Meanwhile, we recently revealed novel regulatory genes involved in the light-dependent regulation in *Streptomyces coelicolor* A3(2).

Light-induced carotenoid production in *Myxococcus xanthus*

Myxobacteria are Gram-negative rods found in soil, dung, decaying plants and on the barks of trees [27]. These organisms have received considerable attention because of a number of interesting features such as gliding motility and cellular development. Many Myxobacteria produce pigments; some pigments are made constitutively, while others include carotenoids that are formed upon illumination [10, 27]. Among the carotenoid-producing strains, *M. xanthus* has been chosen as a model to study the complex molecular mechanism that controls transcriptional initiation of the carotenoid biosynthesis gene cluster (Fig. 1). In the dark, the extracytoplasmic function (ECF) sigma factor CarQ is sequestered by CarR, which is a membrane-bound anti-sigma factor [18]. Illumination inactivates CarR through CarF, such that CarQ is released and initiates the transcription of the *carQRS* operon and *crtI* [15]. The expressed CarS sequesters CarA, which represses the *crt* operon in the dark, such that the transcription of carotenoid biosynthesis genes is initiated and the corresponding enzymes are produced [52]. The entire mechanism in *M. xanthus* appears much more complex; for example, transcription from the *carQRS* promoter requires the additional expression of *ihfA* and *carD*, which encode an alpha subunit of the integration host factor and a high mobility group A (HMGA) DNA-binding protein, respectively [16, 39]. Unlike the mechanism identified in *S. coelicolor* A3(2), as described below, there is no in vitro evidence for the transcription of the carotenoid biosynthesis operon driven by the ECF sigma factor σ^{CarQ} in *M. xanthus* [9].

Carotenogenesis in *Streptomyces*

The soil-inhabiting Gram-positive bacterial genus *Streptomyces* is characterized by the ability to perform

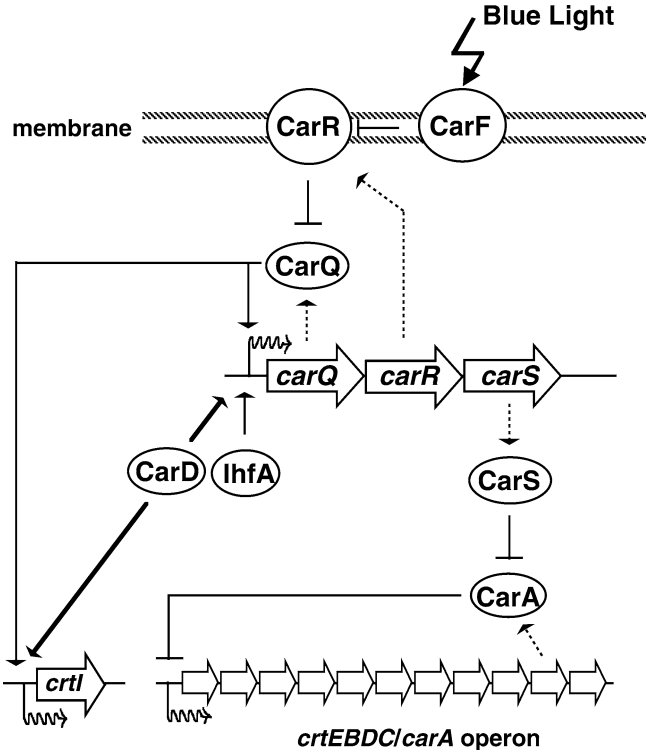

Fig. 1 Light-induced transcriptional control for *M. xanthus* carotenogenesis. Genes are represented as *open arrows* and proteins as *ovals*. Positive regulation and negative regulation are represented by *continuous arrows* and *blunt-ended lines*, respectively. The carotenoid biosynthesis genes are encoded by *crtI* and *crtEBDCI carA* operons. The *carQRS* operon codes for CarQ (an ECF sigma factor), CarR (a membrane-bound anti-sigma factor of CarQ) and CarS (the antirepressor of CarA). While IhfA (the alpha-subunit of the integration host factor) is required for *carQRS* transcription, CarD (an HMGA-like protein) is required for *crtI* as well as *carQRS* expressions. CarF, an unknown protein, is involved in the light-dependent inactivation of CarQ [15]

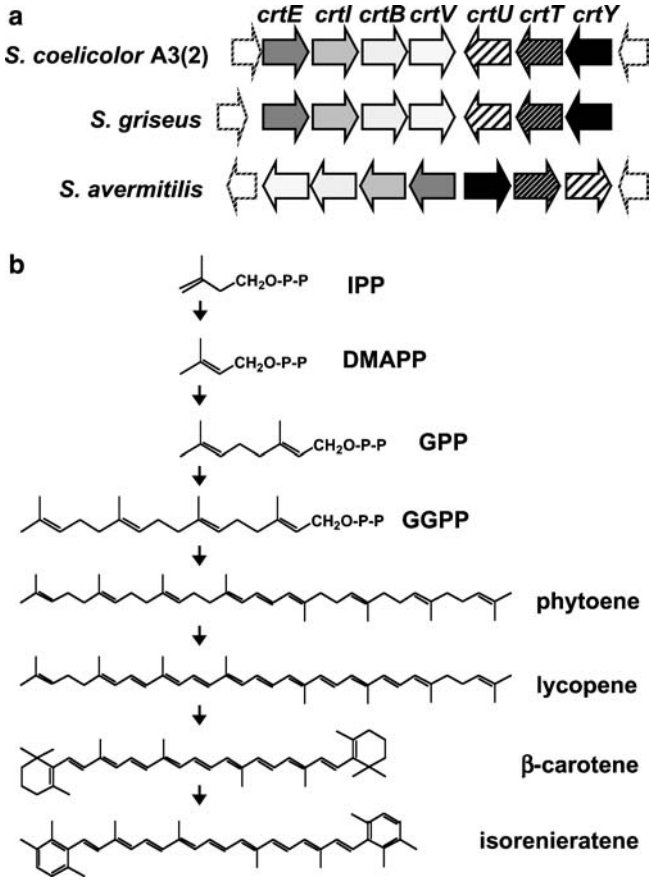

Fig. 2 Biosynthesis gene clusters (**a**) and pathway (**b**) for carotenogenesis in *Streptomyces* spp. **a** The gene clusters of *S. coelicolor* A3(2), *S. griseus* and *S. avermitilis* are shown. The clusters consist of two operons, *crtEIBV* and *crtYTU*, which have convergent orientations in *S. coelicolor* and *S. griseus* and divergent orientations in *S. avermitilis*. **b** The reaction catalysed by each Crt biosynthesis enzyme is shown. Abbreviations used are: *IPP* isopentenyl pyrophosphate; *DMAPP* dimethylallyl pyrophosphate; *GPP* geranyl pyrophosphate; and *GGPP* geranylgeranyl pyrophosphate

complex morphological differentiation resembling that of filamentous fungi as well as by the ability to produce a wide variety of secondary metabolites [13]. The biologically active compounds produced by these organisms, which include antibiotics and antitumour substances, have important industrial applications [38]. To date, the complete genomic sequences of two *Streptomyces* strains, *S. coelicolor* A3(2) (http://www.sanger.ac.uk/Projects/S_coelicolor) [6] and *Streptomyces avermitilis* (http://avermitilis.ls.kitasato-u.ac.jp) [25], have been reported. The sequence databases indicate that both the organisms retain carotenoid biosynthetic gene clusters (Fig. 2a). In addition, Lee et al. [34] have reported the cloning of a carotenoid biosynthesis gene cluster of *S. griseus*, which has a gene organization identical to that of *S. coelicolor* A3(2).

The biosynthesis gene clusters of the above three *Streptomyces* spp. generally retain the coding sequences for seven biosynthesis enzymes: CrtE, geranylgeranyl pyrophosphate synthase; CrtI, phytoene dehydrogenase; CrtB, phytoene synthase; CrtV, functionally unknown methyltransferase; CrtU, β-carotene dehydrogenase; CrtT, functionally unknown methyltransferase; and CrtY, lycopene cyclase. The seven Crt proteins are widely distributed among bacteria and constitute a set of carotenoid enzymes which catalyse the biosynthesis pathway shown in Fig. 2b [2, 3]. Our isolation study has confirmed the presence of β-carotene and isorenieratene in the cell extract of *S. coelicolor* A3(2) [49].

In *Streptomyces*, carotenoid production occurs in a constitutive, light-dependent or cryptic manner [29]. This suggests the diversity of the regulatory mechanisms for carotenoid production in these bacteria. To date, the genetic study on carotenoid production in *Streptomyces* has been performed with *S. griseus* [34, 46], *S. setonii* [28] and *S. coelicolor* A3(2) [49]. The carotenoid production in the former two strains does not occur in any known culture condition but is induced when a high-copy-number plasmid that carries CrtS, a stress-response sigma factor, is introduced into the cells [28, 34]. The evidence implies that the sigma factor is involved in the regulation of carotenoid production in these organisms,

but its expression or activation mechanism is unknown. On the other hand, we have found that *S. coelicolor* A3(2) performs carotenogenesis in a light-induced manner [49].

Photo-induced transcriptional regulation of *crt* cluster in *S. coelicolor* A3(2)

Our study has revealed novel regulatory genes that are involved in the photo-induced expression of the carotenoid biosynthesis genes in *S. coelicolor* A3(2) [49]. The carotenoid biosynthesis gene cluster of this organism is flanked by a regulatory region. This region contains five coding sequences that encode the following proteins: LitQ, a possible oxidoreductase; LitR, a MerR-type transcriptional regulatory protein; LitS, an ECF sigma factor; LitA, a possible lipoprotein; and LitB, a possible anti-sigma factor protein. Our genetic and biochemical study on the regulatory locus has revealed that σ^{LitS} serves as a specific sigma factor for the transcription from the two convergent promoters of the *crt* biosynthesis gene cluster (P*crtE* and P*crtY*) (Fig. 3). The transcription of *litS* is induced by light, and the induction depends on the function of σ^{LitS} and LitR [49]. We recently discovered that the introduction of *litR* and *litS* into *S. griseus* by using a plasmid successfully reproduced the light-dependent transcription from P*crtY*, which was also cloned onto the plasmid (unpublished result). The observation of heterologous gene expression in *S. griseus*, which does not perform light-induced carotenogenesis by itself, raises the possibility that LitR is sufficient for establishing photo-responsive transcriptional control. Namely, it is possible that the protein serves both as a DNA-binding protein as well as a sensor for a chemical signal produced upon illumination.

Possible function of LitR

LitR protein is a MerR family transcriptional regulatory protein. The activities of this family of proteins are regulated by the specific ligand molecules that bind the proteins; for example, MerR that is encoded by several transposons serves as a molecular switch for the expression of mercury resistance by recruiting RNA polymerase holocomplex to the promoter of the mercury resistance operon, and its activity is regulated by the binding of the mercury ion [8]. The putative photo-responsive function of LitR suggests that the ligand is a molecule capable of receiving some signal generated upon illumination. A protein motif search by Pfam program (http://www.sanger.ac.uk/Software/Pfam/) indicates that the carboxy-terminal domain of LitR contains a binding site for vitamin B12 (our unpublished observation). It has been suggested that CarA of *M. xanthus*, which is similar to LitR, also binds vitamin B12 [12]; this is based on its domain similarity to the vitamin B12 proteins and the fact that the light-induced carotenogenesis in *M. xanthus* is clearly observed in the media supplied with vitamin B12. The protein-bound form of vitamin B12 and its related compounds is known to absorb blue light (maximum at 400 nm) [26]. This is consistent with our observation that the carotenoid production in *S. coelicolor* A3(2) is induced by blue light [49]. Elucidation of the biochemical function of the type of transcriptional regulator may provide new insights into the molecular mechanism of light-induced gene expression in non-phototrophic microorganisms. The distribution of the CarA/LitR family proteins in various bacterial genomes and their clustering to putative photo-responsive genes will be described elsewhere.

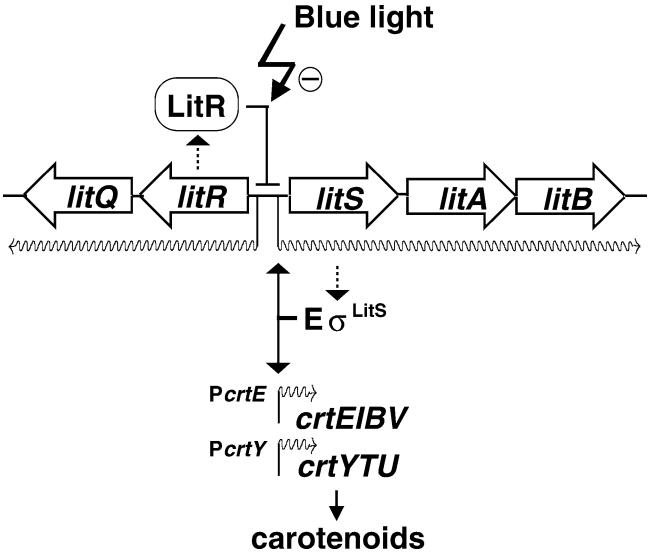

Fig. 3 A working hypothesis for the regulatory mechanism of light-induced carotenoid biosynthesis in *S. coelicolor* A3(2). The transcription of *crt* gene clusters (*crtEIBV* and *crtYTU*) from the two convergent promoters P*crtE* and P*crtY* is driven by an RNA polymerase holocomplex containing σ^{LitS}. The light-induced expression of σ^{LitS} is mediated by LitR, which is a MerR family transcriptional regulator. Possibly, LitR serves as a negative regulator for *litS* as well as *litR* promoters, and its conformational change upon receiving an illumination signal may cause derepression of *litS* transcription

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