

Peer-Review Record:

Terpenoids and Their Biosynthesis in Cyanobacteria

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***Life* 2015, 5, 269-293, doi:10.3390/life5010269**

Reviewer 1: Anonymous

Reviewer 2: Thomas D. Sharkey

Editor: John C. Meeks and Robert Haselkorn (Guest Editor of Special Issue “Cyanobacteria: Ecology, Physiology and Genetics”)

Received: 20 December 2014 / *Accepted:* 14 January 2015 / *Published:* 21 January 2015

First Round of Evaluation

Round 1: Reviewer 1 Report and Author Response

This review covers the most recent status of the knowledge of biosynthesis of terpenes in Cyanobacteria, as well as their use in the heterologous expression of plant terpene biosynthetic pathways. There is currently a need for such a review and the authors highlight several key omissions in the current knowledge in the field. Future work along these lines will help us utilise Cyanobacteria as a sustainable method for the production of various terpenes of commercial interest.

Response: We would like to thank the reviewer for the helpful comments on our manuscript. Below is a list with each comment and the changes we have made.

Below are some minor corrections that need to be addressed.

- Line 191: It is incorrect to state that Cyanobacteria are the oldest organisms on the earth. Perhaps evidence suggests that they are one of the oldest (other chemoautotrophs likely existed at the same time or prior to Cyanobacteria).

Response: The sentence has been corrected.

- Table 1: It is not clear what the numbers in the columns labelled “left” and “right” refer to. I suggest that these columns are not needed? Or perhaps could be replaced with nucleotide or protein sizes?

Response: Table 1 has been updated to show “gene size” instead.

- Line 221: spelling error—*enterica* (not *enteric*)

Response: Corrected.

- Lines 257–259: Cyanobacteria have a wide range of growth rates and vary in their ability to reach high densities in culture. They also vary in their ability to be genetically manipulated. Perhaps this section should be modified to clarify to the reader which strains/species are being referred to here.

Response: The text has been updated to clarify that certain strains, not all, have the mentioned properties.

- Line 298: Insert Lindberg *et al.* here.

Response: Corrected.

- Line 318: Should read “Monoterpenes, due to their small molecular weight, are usually emitted as volatiles ...”

Response: The sentence has been changed.

- Page 15: The gene name for squalene hopene cyclase should be provided (not protein)

Response: The change has been made.

Round 1: Reviewer 2 Report and Author Response

This review compiles a significant amount of work that has been done to develop cyanobacteria as a platform for production of terpenes. Production of terpenes in yeast and nonphotosynthetic bacteria is becoming a commercial reality but there is hope that cyanobacteria can become a platform to take advantage of the energy of sunlight. This way one organism can both harvest the sunlight and make the desired product without making an intermediate sugar in a photosynthetic organism and feeding that sugar to a second organism to make the desired product. The authors cover the production of the universal precursors IDP and DMADP and then the downstream processing required to turn these into C5, C10, and higher order terpenoids. This will be a valuable review for people in the field and should be of interest to others wanting to know the current state of the art for terpene production in cyanobacteria.

Response: We would like to thank the reviewer for the helpful comments on our manuscript. Below is a list with each comment and the changes we have made.

I have some specific suggestions keyed to line numbers.

- I would encourage the authors to go all the way with the diphosphate nomenclature. Isopentenyl diphosphate can be abbreviated IDP, also DMADP, HMBDP, MEcDP. A growing number of people are doing this (as recommended by IUPAC) though it is probably still fewer than 1/2 of the people in the field. Like the transitions of RuDP → RuP2 → RuBP ended in the BP abbreviation becoming standard, I expect eventually it will be IDP *etc.* and we will look back on IPP like we do now on TPN. Compare it to the use of ADP not APP and ATP not APPP.

Response: We agree, and have changed the abbreviations throughout the manuscript and figure.

- Figure 1—The CO₂ is coming off of the GAP line when in fact it comes from pyruvate. Also, only the thylakoids are green. Removing the green background would make the figure more appealing (making the just the thylakoids green will give a nice dash of color).

Response: The figure has been changed.

- Line 132 I have now found convincing evidence that DXP is one of the starting points for thiamin in plants as well as bacteria.

Response: The sentence has been changed and references updated to include plants.

- Line 169—I would not call the process of making linear terpenes from precursors “linearization”. While many enzymes make cyclic products some make linear products and there is not too much difference between linear-terpene synthases and cyclic-terpene synthases. The cyclases do cyclize but the synthases that make linear terpenes such as myrcene synthase and farnesene synthase do not linearize, the starting compound is already linear.

Response: The sentence has been changed.

- Line 187 missing parenthesis

Response: Corrected.

- Line 191 delete “as”

Response: The sentence has been changed, see comment by reviewer 1 above.

- 210 to “that” in *E. coli*

Response: The change has been made.

- 213 personal preference, but I don’t think it is necessary to say “as mentioned above”

Response: The change has been made.

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