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USE OF GENOME-SCALE MODELS TO GET NEW INSIGHTS INTO THE MARINE ACTINOMYCETE GENUS SALINISPORA: MICROBIAL ENGINEERING AND ITS APPLICATION IN SECONDARY METABOLITE PRODUCTION

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The genus *Salinispora* is a source of natural products such as antibiotics and anticancer agents. *Salinispora tropica* is a marine actinomycete that produces diverse secondary metabolites, including many that possess pharmaceutical properties such as Salinosporamide A (NPI-0052), a potent anticancer agent, and sporolides, candidates for antiviral compounds. So far little has been published regarding metabolism of Salinispora species. This study is focused on new insights into the metabolism of the three-identified species of Salinispora using constraints-based modeling. Up to now, only one manually curated genome-scale metabolic model (GSM) for *Salinispora tropica* strain CNB-440T has been built despite the role of Salinispora strains in drug discovery (1).

We have updated, and expanded the model of *Salinispora tropica C*NB-440T, and Genome-scale Models (GSMs) were constructed for two sequenced type strains covering the three-identified species. We have also constructed a Salinispora core model that contains the genes shared by 93 sequenced strains (2). The models predicted no auxotrophies for essential amino acids, which was corroborated experimentally using a defined minimal medium (DMM). The core metabolic content shows that the biosynthesis of specialised metabolites is the less conserved subsystem. Sets of reactions were analyzed to explore the differences between the reconstructions.

Unique reactions associated to each GSM were mainly due to genome sequence data except for the ST-CNB440 reconstruction. In this case, additional reactions were added from experimental evidence. This reveals that by reaction content the ST-CNB440 model is different from the other species models. The differences identified between models gave rise to different functional predictions of essential nutrient usage by each species in DMM. Furthermore, models were used to evaluate in silico single gene knockouts in DMM and complex medium.

These models allow in silico metabolism studies of Salinispora strains, and can be used to increase the production of specialized metabolites such as Salinisporamide A (at least 20% compared to the wild type). Also, models can be used as templates to build GSMs models of closely related organisms with high biotechnological potential.

(1) Contador CA, Rodríguez V, Andrews BA, Asenjo JA. (2015) Genome-scale reconstruction of Salinispora tropica CNB-440 metabolism to study strain-specific adaptation. Antonie van Leeuwenhoek, Int. J. Gen. Mol. Microbiol.,108:1075–90.

(2) Contador CA, Rodríguez V, Andrews BA, Asenjo JA. (2019) Use of Genome Scale Models to get New Insights into the Marine Actinomycete genus Salinispora. BMC systems Biology, 13, 11.