Genome-scale metabolic modeling of a minimized Streptomyces strain

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Overview

Streptomyces a genus of filamentous soil bacteria from the phylum *Actinobacteria,* is widely known for its diverse machinery of secondary metabolite production. The bacteria are excellent hosts for the heterologous expression of complex natural compounds. To explore the biological constraints of a minimalized mutant of *Streptomyces avermitilis,* we use a high quality genome-scale metabolic model with over 4,000 reactions and 2,400 metabolites. It is based on annotated genes, as well as physiological and biochemical information. This model allows for the in-depth understanding of the metabolic fluxes and context of the metabolic network. This information is used for the genetic optimization of the host to increase yields of heterologous expressed complex natural drugs such as griseorhodin A.

Rubromycines

Rubromycines, such as griseorhodin A, have been known for their vivid red colors since the 60‘s and are characterized by a spiroketal moiety. They show promising activity against HIV reverse trancriptase and human telomerase. Although extensive efforts towards their total synthesis have been undertaken, the available synthetic routes are still limited.[1]

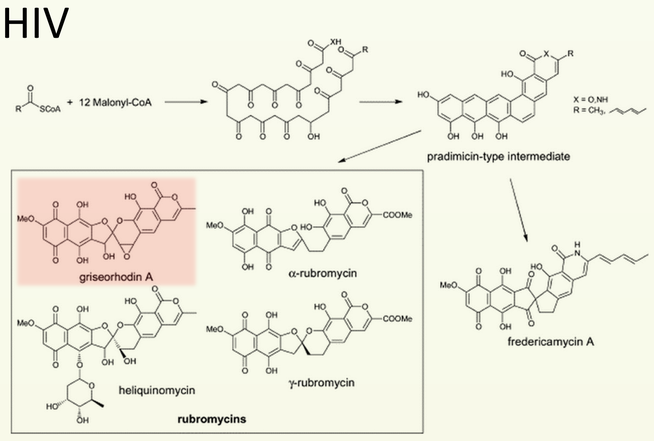

Fig1: Rubromycines and their biosynthesis[2]

Host strains

Streptomycetes are excellent hosts for heterologous expression of secondary metabolites. The group of Prof. H. Ikeda has developed a genomically minimized mutant of the industrially used strain *S. avermitilis*. These SUKA strains have proven superior to many natural hosts in terms of secondary metabolite production.[3]

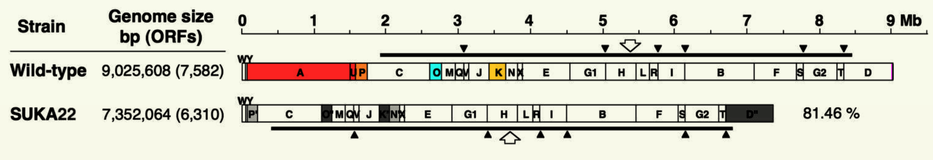

Fig2: S. avermitilis wild-type genome compared to SUKA 22 strain modified from Komatsu et al.[3]

Metabolic modeling

Genome-scale metabolic models offer deep insights in the complex network of reactions that is needed to maintain life and produce secondary metabolites. Combined with experimental data, such as gene expression levels, they allow for the identification of the key players that can be addressed to increase the overall efficiancy of secondary metabolite production.[4]

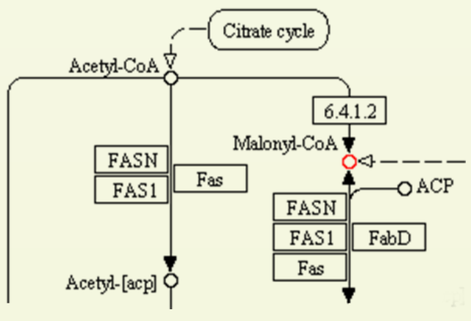

Fig3: KEGG: section of the fatty acid synthesis

Cofactor availability

Besides the generation of the carbon backbone, cofactor availability plays a crucial role in the synthesis of most secondary metabolites. However, regulation of certain pathways can cause an imbalance of cofactors, whereby the efficiancy of other pathways can be impared. Hence, the analysis and understanding of the cofactors distribution and regeneration systems is an important step towards the development of an efficient producer of natural compounds.[5]

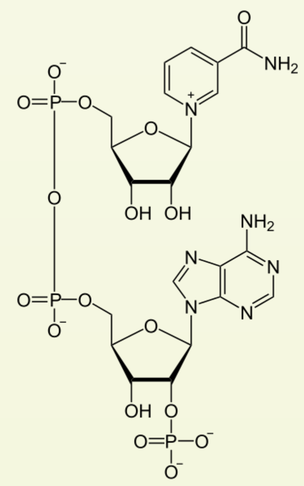

Fig4: NADP: hydride transferring cofactor

Conclusion

Metabolic models are powerful tools for the analysis of the supply and role of substrates, precursors, and cofactors. By the generation of insights in the fluxes of metabolites and energy equivalents, the combination of the described resources and methods aims at an establishment of an effective heterologous expression system for griseorhodin A.

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