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Poster presentation

Metabolic flux analysis for directing metabolism of *Streptomyces olindensis* from growth to anti-tumor drug (cosmomycin) production

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Introduction

The aim of this work is to develop a computational model based on metabolic flux balancing methodology for the primary metabolism of *Streptomyces olindensis* and the biosynthesis of cosmomycin so that metabolic shifts in directing metabolism from growth to cosmomycin production can be investigated.

Background

Cosmomycin, an aromatic polyketide antibiotic complex produced by *Streptomyces olindensis*, belongs to anthracycline family of chemotherapy drugs. It is a powerful anti-tumor drug similar to doxorubicin and daunorubicin. The structure of cosmomycin consists of one tetracycline aglycon (β-rhodomycinone) and six deoxysugars (two dTDP-L-2-deoxifucose, two dTDP-L-rodosamine and two dTDP-L-rodinose). The tetracycline aglycon, a polyketide structure, is obtained by condensation of one propionyl-CoA with nine acetate molecules derived from malonyl-CoA by the action of enzymes known as minimal Polyketide Synthetases (minimal PKS).

Model construction

The *in silico* metabolism was reconstructed involving more than 240 stoichiometrically balanced metabolic reactions in matrix formalism using the information from the literature and databases (top-down and bottom-up). Then, computational metabolic flux balancing method was used in order to obtain fluxes of all the metabolic reactions with linear programming and optimisation in GAMS environment (General Algebraic Modeling System). The objective function of optimisation was either the maximisation of the specific growth rate or the maximisation of the specific cosmomycin production rate. The experimental specific glucose uptake and growth rates were used as the model constraints, as appropriate. The solution of the metabolic model gave the specific growth and/or product formation rates as well as the specific rates of all 242 metabolic reactions.

Results

The comparison of internal metabolite fluxes between the maximisation of specific growth and cosmomycin production revealed important changes in fluxes related to energy production and redox balances (NADH, FADH2,

and ATP), as well as oxygen consumption and CO2 generation when the metabolism shifts from growth to cosmomycin production. In addition, there was an important change in the fluxes of the TCA intermediates. This indicates that during growth maximisation more energy is required, so the TCA cycle is complete, more active and the aerobic respiration rate is increased. Another important observation is in the acetyl-CoA flux; during growth maximisation, this metabolite enters the TCA cycle but during cosmomycin maximisation all acetyl-CoA goes to malonyl-CoA, the precursor of this antibiotic. The TCA cycle is not complete in this case and depends on the anaplerotic reactions and 3-phosphoglycerate. The sensitivity analysis performed in GAMS also confirms this. This also highlights the reason for the inclusion of casamino acids in the culture medium in the experiments. Another important change is observed in the glucose-1P flux because during growth maximisation it goes to carbohydrate biosynthesis and during cosmomycin production it goes to this product.

Conclusion

The results of the model and the experiments for growth and cosmomycin production are in reasonable agreement which means that this model can be used to identify strategies for directing the metabolism from growth to secondary metabolism.

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