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Metabolic flux analysis to study the production of a non-ribosomal lipopeptide, CDA, by *Streptomyces coelicolor*

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Background

The Calcium Dependent Antibiotic (CDA) from *S. coelicolor* is a non-ribosomally synthesised lipopeptide which consists of 11 amino acids to which a lipid part has been attached [1]. Although the mode of action for CDA is not yet known, antibiotics with similar structure like daptomycin or friulimicin inhibit bacterial cell wall synthesis. CDA-related drugs therefore, may become very important in treating infections from severe antibiotic resistant pathogens, such as methicillin-resistant *Staphylococcus aureus* strains (MRSA) and vancomycin-resistant enterococci (VRE). CDA contains several nonproteinogenic amino acids, crucially L-4-hydroxyphenylglycine (HPG). This amino acid is also present in the backbone of various important therapeutics such as; peptides (complestatin and nocardicin), glycopeptides, (vancomycin and teicoplanin), further lipopeptides (arylomycin), and the lipoglycodepsipeptide antibiotic ramoplanin.

Model construction

In this work, a metabolic model for *S. coelicolor* was constructed using the metabolic flux analysis approach [2]. The metabolic model involved around 250 reactions of the primary and secondary metabolism leading to CDA formation. We used the model for *in silico* experimentation and prediction of the internal metabolite fluxes under different conditions during *S. coelicolor* fermentation, either for the maximisation of growth or CDA production using linear programming in GAMS software.

Results

The comparison of internal metabolite fluxes between the maximisation of growth and CDA production revealed important changes in fluxes related to NADPH (Pentose Phosphate pathway), CDA amino acid precursors (serine, glycine, HPG and tryptophan) and NADH. We are now using this model in predictive mode in order to develop strategies to increase CDA productivity; such as, media formulation, precursor addition and identification of genetic engineering targets.

Conclusion

Computational metabolic flux analysis can be used in order to study the interrelationship between the primary metabolism and biosynthetic pathways for CDA, as well as for the *in silico* experimentation for the identification of genetic engineering targets for increased production. It can also be used to investigate any precursor effects for precursor-directed biosynthesis combined with genetic engineering.

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