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INTEGRATION OF TRANSCRIPTOMIC DATA WITH A GENOME-SCALE MODEL REVEALS KEY METABOLIC FEATURES OF HIGH PRODUCER CHO CELL LINES

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The increasing demand for therapeutic proteins has been a driving force for the development of new strategies to improve cellular productivity. Common approaches rely on targeting genes involved in pathways related to cell cycle, central metabolism, apoptosis and protein secretion. However, despite several experimental efforts, cellular processes underpinning high-productivity cell clones remain poorly understood.

In order to identify novel potential targets associated to high recombinant protein synthesis, we employed a systems biology approach using transcriptomics data in CHO IgG producing cells. This approach was further integrated with a genome-scale metabolic model, enabling integration of this high-throughput data and providing a rational framework for target discovery.

The reconstructed CHO genome-scale model accounts for 1,272 genes, and 3,646 reactions distributed among 7 cell compartments. We then integrated the metabolic model with transcriptomic data from two CHO antibody producer cell lines. To this task, iMAT (Integrative Metabolic Analysis Tool) was used to reduce the initial CHO reconstruction to represent two scenarios: a high and a low producer cell line. This algorithm maximizes the consistency with experimental data without requiring the definition of a biological objective in order to give models and flux distributions that represent both CHO cell clones.

In this way, an initial reduction to 840 reactions was achieved from the high producer clone which includes 183 reactions exclusively present in this CHO cell line. Application of uniform random sampling to both CHO models confirmed some of the above targets and furthermore, revealed novel metabolic insights related to antibody production. Overall, integration of transcriptomic data with a genome-scale metabolic model provides a rational framework to improve CHO metabolism for recombinant protein production.