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A COMMUNITY GENOME-SCALE MODEL OF CHINESE HAMSTER OVARY CELL METABOLISM IDENTIFIES DIFFERENCES IN THE EFFICIENCY OF RESOURCE UTILIZATION FOR VARIOUS BIOPROCESSES

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Genome-scale models of metabolism have successfully been employed in many microbial and eukaryotic metabolic engineering efforts by guiding pathway engineering and media optimization. They have also been used to explore the genotype-phenotype relationship in mammalian cells. The publication of the genomic sequence for Chinese hamster ovary (CHO) cells has allowed generation of genome-scale metabolic models (GeMs) for this organism. Here we have developed a high-quality community CHO GeM via careful reconciliation and manual curation of three independently developed CHO GeMs. This metabolic model, consisting of over 4000 metabolites and 6000 reactions, is capable of integrating proteomic, transcriptomic, and metabolomic data and can accurately simulate experimentally measured growth rates. Integration of transcriptomic and proteomic data from CHO-K1 and CHO-S shed light on the enzymatic basis for various amino acid auxotrophies characteristic of the cell lines. We show that experimental arginine and cysteine auxotrophies are recapitulated by model predictions (via reaction inactivation) while the characteristic proline auxotrophy is not, due to detectable levels of expression in biosynthetic pathways for this amino acid. We additionally used the model to assess the metabolic limitations on recombinant protein producing lines subject to different cell line and process modifications and found that some alterations result in specific productivities up to 20-fold lower than computational predictions of metabolically feasible production rates. The results indicate a possible secretory bottleneck and implicate engineering the secretory pathway as a lucrative target to pursue in future CHO cell line engineering.