Chinese hamster ovary (CHO) cells dominate biotherapeutic protein production and are widely used in mammalian cell line engineering research. To elucidate metabolic bottlenecks in protein production and to guide cell engineering and bioprocess optimization, we reconstructed the metabolic pathways in CHO and associated them with >1,700 genes in the Cricetulus griseus genome. The genome-scale metabolic model based on this reconstruction, iCHO1766, and cell-line-specific models for CHO-K1, CHO-S, and CHO-DG44 cells provide the biochemical basis of growth and recombinant protein production. The models accurately predict growth phenotypes and known auxotrophies in CHO cells. With the models, we quantify the protein synthesis capacity of CHO cells and demonstrate that common bioprocess treatments, such as histone deacetylase inhibitors, inefficiently increase product yield. However, our simulations show that the metabolic resources in CHO are more than three times more efficiently utilized for growth or recombinant protein synthesis following targeted efforts to engineer the CHO secretory pathway. This model will further accelerate CHO cell engineering and help optimize bioprocesses.

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