Genome-scale modeling of CHO cells unravel the critical role of asparagine in cell culture feed media

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Abstract

Amino acids, including asparagine, aspartate, glutamine, and glutamate, play important roles in the purine and pyrimidine biosynthesis as well as serve as anaplerotic sources fueling the tricarboxylic acid (TCA) cycle for mitochondrial energy generation in mammalian cells. Despite extensive studies on glutamine and glutamate in CHO cell cultures, the roles of asparagine and aspartate, especially in feed media, remain underexplored. In this study, we utilized the CHO genome scale model to first deeply characterize the intracellular metabolic states of CHO cells cultured in different combinations of basal and feed media to understand the traits of asparagine/aspartate-dependent and glutamate-dependent feeds. Subsequently, we identified the critical role of asparagine and aspartate in the feed media as anaplerotic sources and conduct in silico simulations to ascertain their optimal ratios to improve cell culture performance. Finally, based on the model simulations, we reformulated the feed media by tailoring the concentrations of asparagine and aspartate. Our experimental data reveal a CHO cell preference for asparagine compared with aspartate, and thus maintaining an optimal ratio of these amino acids is a key factor for achieving optimal CHO cell culture performance in biopharmaceutical production.

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