Multi-omic profiling of EPO-producing Chinese hamster ovary cell panel reveals metabolic adaptation to heterologous protein production - DTU Orbit (17/12/2018)

**Multi-omic profiling of EPO-producing Chinese hamster ovary cell panel reveals metabolic adaptation to heterologous protein production**

Chinese hamster ovary (CHO) cells are the preferred production host for many therapeutic proteins. The production of heterologous proteins in CHO cells imposes a burden on the host cell metabolism and impact cellular physiology on a global scale. In this work, a multi-omics approach was applied to study the production of erythropoietin (EPO) in a panel of CHO-K1 cells under growth-limited and unlimited conditions in batch and chemostat cultures. Physiological characterization of the EPO-producing cells included global transcriptome analysis, targeted metabolome analysis, including intracellular pools of glycolytic intermediates, NAD(P)H/NAD(P)+, adenine nucleotide phosphates (ANP), and extracellular concentrations of sugars, organic acids, and amino acids. Potential impact of EPO expression on the protein secretory pathway was assessed at multiple stages using quantitative PCR (qPCR), reverse transcription PCR (qRT-PCR), Western blots (WB), and global gene expression analysis to assess EPO gene copy numbers, EPO gene expression, intracellular EPO retention, and differentially expressed genes functionally related to secretory protein processing, respectively. We found no evidence supporting the existence of production bottlenecks in energy metabolism (i.e., glycolytic metabolites, NAD(P)H/NAD(P)+ and ANPs) in batch culture or in the secretory protein production pathway (i.e., gene dosage, transcription and post-translational processing of EPO) in chemostat culture at specific productivities up to 5 pg/cell/day. Time-course analysis of high- and low-producing clones in chemostat culture revealed rapid adaptation of transcription levels of amino acid catabolic genes in favor of EPO production within nine generations. Interestingly, the adaptation was followed by an increase in specific EPO productivity.

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