METABOLOMICS APPROACH FOR INCREASING CHO CELL SPECIFIC PRODUCTIVITY

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Chinese hamster ovary cells are the most commonly used expression system in the production of monoclonal antibody therapeutic drugs. The biomanufacturing industry has made significant advances in increasing protein titers of these cell cultures by over 100-fold since the 1980s to gram-per-liter ranges, and much of this progress has been made via increasing cell density and viability. However, even next generation processes are approaching the limits of how high cell densities can be reached with available technologies. On the other hand, the specific productivity (qP) of the cell lines, though much higher now than at the advent of biologics production, has not been improved to the same degree, and advances on this front are needed to attain higher titers in shorter times. In this work, a library of twelve cell lines, having a wide range of qPs but all derived from the same parental cell line and expressing one of two different antibodies, was investigated using an untargeted metabolomics approach. Spent medium samples were collected from each fed-batch culture at two time points. BioCAn (Biologically Consistent Annotation), a recently developed automated annotation tool, was used to determine the most likely identities of features detected in LC-MS data from these cell lines. A correlation analysis was then performed to find annotated features that were significantly associated with either cell growth (37 features), qP (32 features), or both (56 features). Interestingly, all features associated with cell growth showed a negative correlation, while all features associated with qP showed a positive correlation. To investigate whether metabolites positively correlated with qP reflect endogenous metabolic activity beneficial for productivity, several metabolites were added to the culture medium at varying concentrations. We found that supplementing the medium with one or more select metabolites could improve qP without negatively impacting cell growth. We next evaluated whether these metabolites could be used as biomarkers to identify clones with potential for high productivity, as current screening methods can falsely eliminate clones due to sub-optimal culture media or process conditions. Together, these studies demonstrate opportunities for using untargeted metabolomics to achieve higher titer in biologics production processes. Further, the identification of biomarkers has potential to shorten cell line development timelines, which is on the critical path to biologics manufacturing.