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The development of next-generation sequencing technologies has opened new opportunities to better characterize complex eukaryotic cells. Chinese hamster ovary (CHO) cells play a primary role in therapeutic protein production, with currently five of the top ten blockbuster drugs produced in CHO. However, engineering superior CHO cells with improved production features has had limited success to date and cell lines are still developed through the generation and screening of large strain pools. Here, we applied RNA sequencing to contrast a high and a low monoclonal antibody producing cell line. Rigorous experimental design achieved high reproducibility between biological replicates, remarkably reducing variation to less than 10%. More than 14000 gene-transcripts are identified and surprisingly 58% are classified as differentially expressed, including 2900 with a fold change higher than 1.5. The largest differences are found for gene-transcripts belonging to regulation of apoptosis, cell death, and protein intracellular transport GO term classifications, which are found to be significantly enriched in the high producing cell line. RNA sequencing is also performed on subclones, where down-regulation of genes encoding secreted glycoproteins is found to be the most significant change. The large number of significant differences even between subclones challenges the notion of identifying and manipulating a few key genes to generate high production CHO cell lines.

General information
Publication status: Published
Organisations: Novo Nordisk Foundation Center for Biosustainability, Quantitative Modeling of Cell Metabolism, University of Queensland
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Number of pages: 10
Publication date: 2018
Peer-reviewed: Yes

Publication information
Journal: Biotechnology Journal
Volume: 13
Issue number: 3
ISSN (Print): 1860-6768
Ratings:
BFI (2018): BFI-level 1
Scopus rating (2018): CiteScore 3.61 SJR 1.17 SNIP 0.943
Web of Science (2018): Impact factor 3.543
Web of Science (2018): Indexed yes
Original language: English
DOIs:
10.1002/biot.201700231
Source: Findit
Source ID: 2395319776
Research output: Contribution to journal › Journal article – Annual report year: 2018 › Research › peer-review