Impact of CHO Metabolism on Cell Growth and Protein Production: An Overview of Toxic and Inhibiting Metabolites and Nutrients

For over three decades, Chinese hamster ovary (CHO) cells have been the chosen expression platform for the production of therapeutic proteins with complex post-translational modifications. However, the metabolism of these cells is far from perfect and optimized, and requires substantial knowhow and process optimization and monitoring to perform efficiently. One of the main reasons for this is the production and accumulation of toxic and growth-inhibiting metabolites during culture. Lactate and ammonium are the most known, but many more have been identified. In this review, we present an overview of metabolites that deplete and accumulate throughout the course of cultivations with toxic and growth inhibitory effects to the cells. We further provide an overview of the CHO metabolism with emphasis to metabolic pathways of amino acids, glutathione (GSH), and related compounds which have growth-inhibiting and/or toxic effect on the cells. Additionally, we survey relevant publications which describe the applications of metabolomics as a powerful tool for revealing which reactions occur in the cell under certain conditions and identify growth-inhibiting and toxic metabolite. We also present a number of resources that describe the cellular mechanisms of CHO and are available on-line. Finally, we discuss the application of this knowledge for bioprocess and medium development and cell line engineering.

Reprogramming amino acid catabolism in CHO cells with CRISPR-Cas9 genome editing improves cell growth and reduces by-product secretion

CHO cells primarily utilize amino acids for three processes: biomass synthesis, recombinant protein production and catabolism. In this work, we disrupted 9 amino acid catabolic genes participating in 7 different catabolic pathways, to increase synthesis of biomass and recombinant protein, while reducing production of growth-inhibiting metabolic by-products from amino acid catabolism.
CHO On A Detox: Removing By-Product Formation Through Cell Engineering

Chinese Hamster Ovary (CHO) cells are the preferred hosts for the production of therapeutic glycoproteins. However, there is a need for improvement of the bioprocesses towards increased cell growth and higher productivities without compromising the product quality. Efforts to obtain tailor-made products with the desired properties that meet the requirements of regulatory authorities are continuously being made. Of equal relevance is to develop methods to engineer cell lines with improved by-product metabolism.

General information

Publication status: Published
Organisations: Novo Nordisk Foundation Center for Biosustainability, CHO Cell Line Engineering and Design, Department of Biotechnology and Biomedicine, Network Engineering of Eukaryotic Cell factories
Contributors: Pereira, S., Kildegaard, H. F., Andersen, M. R.
Number of pages: 1
Publication date: 2016
Peer-reviewed: Yes
Event: Abstract from 1st ESACT Frontiers Retreat, Lyon, France.
Electronic versions:
1st_ESACT_Frontiers_RetreatS.Pereira_Abstract.pdf
Research output: Contribution to conference → Conference abstract for conference – Annual report year: 2017 → Research → peer-review

Projects:

Engineering of a by-product-reduced CHO cell line (CleanCHO)
Domingues Pereira, S. I., PhD Student, Novo Nordisk Foundation Center for Biosustainability
Andersen, M. R., Main Supervisor
Kildegaard, H. F., Supervisor
Jensen, M. K., Examiner
Åkesson, M. F., Examiner
Chotteau, V., Examiner
Marie Curie (EU-stipendium)
15/09/2015 → 09/11/2018
Award relations: Engineering of a by-product-reduced CHO cell line (CleanCHO)
Project: PhD

Engineering nutrient and by-product metabolism
Domingues Pereira, S. I., PhD Student, Novo Nordisk Foundation Center for Biosustainability, CHO Cell Line Engineering and Design
Kildegaard, H. F., Supervisor, Novo Nordisk Foundation Center for Biosustainability, CHO Cell Line Engineering and Design
Andersen, M. R., Main Supervisor, Department of Systems Biology, Network Engineering of Eukaryotic Cell Factories
15/09/2015 → 14/09/2018
Project: Research
eCHO Systems: Enhancing CHO by Mammalian Systems Biotechnology
Innovative Training Network (ITN) under Horizon 2020
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FP7 Contract ID: 642663
Horizon 2020
01/01/2015 → 31/12/2018
Keywords: synthetic biotechnology, cell factory optimization, systems biology, industrial biotechnology, biopharmaceuticals
Award relations: Enhancing CHO by Mammalian Systems Biotechnology
Project: Research

Activities:

Metabolic Engineering 12
Period: 24 Jun 2018 → 28 Jun 2018
Sara Isabel Domingues Pereira (Participant)
Novo Nordisk Foundation Center for Biosustainability
CHO Cell Line Engineering and Design

Related event

Metabolic Engineering 12
24/06/2018 → 28/06/2018
Munich, Germany
Activity: Attending an event › Participating in or organising a conference

Reduced by-product and improved cell growth in Chinese Hamster Ovary cells through the engineering of amino acid catabolism
Period: 24 Jun 2018 → 28 Jun 2018
Sara Isabel Domingues Pereira (Other)
Novo Nordisk Foundation Center for Biosustainability
CHO Cell Line Engineering and Design

Description
Poster presentation
Degree of recognition: International

Related event

Metabolic Engineering 12
24/06/2018 → 28/06/2018
Munich, Germany
Activity: Talks and presentations › Conference presentations

Engineering by-product reduced CHO cells
Period: 7 Jun 2018 → 8 Jun 2018
Sara Isabel Domingues Pereira (Speaker)
Novo Nordisk Foundation Center for Biosustainability
CHO Cell Line Engineering and Design
Description
Talk at Animal Cell Technology Industrial Platform (ACTIP) Summer meeting

Related event

ACTIP meeting
07/06/2018 → 08/06/2018
Düsseldorf, Germany
Keywords: Animal cell technology
Activity: Talks and presentations › Talks and presentations in private or public companies and organisations

12th DANISH CONFERENCE ON BIOTECHNOLOGY AND MOLECULAR BIOLOGY (DCB12)
Period: 1 Jun 2017 → 2 Jun 2017
Sara Isabel Domingues Pereira (Speaker)
Novo Nordisk Foundation Center for Biosustainability
CHO Cell Line Engineering and Design

Description
CRISPR-based technologies and Bio-products
Participation with a poster.
Degree of recognition: National

Related event

12th DANISH CONFERENCE ON BIOTECHNOLOGY AND MOLECULAR BIOLOGY (DCB12): CRISPR-based technologies and Bio-products
01/06/2017 → 02/06/2017
Vejle, Denmark
Activity: Talks and presentations › Conference presentations

Engineering CHO cell’s amino acid metabolism using CRISPR/Cas9 towards optimal by-product and cell growth phenotypes
Period: 1 Jun 2017 → 2 Jun 2017
Sara Isabel Domingues Pereira (Speaker)
Novo Nordisk Foundation Center for Biosustainability
CHO Cell Line Engineering and Design

Description
Poster award (2nd place) and oral presentation
Degree of recognition: National

Related event

12th DANISH CONFERENCE ON BIOTECHNOLOGY AND MOLECULAR BIOLOGY (DCB12): CRISPR-based technologies and Bio-products
01/06/2017 → 02/06/2017
Vejle, Denmark
Keywords: CHO, CRISPR, Genome editing
Activity: Talks and presentations › Conference presentations

1st ESACT Frontiers Retreat
Sara Isabel Domingues Pereira (Participant)
Novo Nordisk Foundation Center for Biosustainability
CHO Cell Line Engineering and Design

Description
Poster presentation
Documents:
1st ESACT Frontiers Retreat
S.Pereira_ Abstract

Related event

1st ESACT Frontiers Retreat
20/10/2016 → 22/10/2016
Lyon, France
Keywords: CHO cells, Chinese hamster ovary, CRISPR-Cas9, metabolism
Activity: Attending an event › Participating in or organising a conference

Prizes:

2nd Poster Prize
Sara Isabel Domingues Pereira (Recipient)
Novo Nordisk Foundation Center for Biosustainability, CHO Cell Line Engineering and Design

Details
Awarded date: 2 Jun 2017
Degree of recognition: National
Granting Organisations: Danish Biotechnological Society
event: 12th DANISH CONFERENCE ON BIOTECHNOLOGY AND MOLECULAR BIOLOGY (DCB12)
Keywords: CHO, eCHO, Genome editing, CRISPR
Prize: Prizes, scholarships, distinctions

ACTIP Fellowship
Sara Isabel Domingues Pereira (Recipient)
Novo Nordisk Foundation Center for Biosustainability, CHO Cell Line Engineering and Design

Details
Awarded date: 8 Jun 2018
Granting Organisations: Animal cell Technology Industrial Platform (ACTIP)
Prize: Prizes, scholarships, distinctions