UCMR
Umeå Centre for Microbial Research

UHRF
Umeå Hypoxia Research Facility

1ST UMEÅ INTERDISCIPLINARY SYMPOSIUM ON HYPOXIC BIOLOGY. MAY 25TH, 2021

Michael Jetten - Microbial ecology
Emilio Bueno - Infection biology
Francesco Licausi - Plant biology
Emily Flashman - Plant biology
Jonathan Gilthorpe - Neurobiology
Randall Johnson - Tumor biology
Jane McKeating - Virology
Robert A Cramer - Fungal biology
Constantin Urban - Fungal biology
Björn Schröder - Gut microbiome
Andreas Baumler - Gut microbiome

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1st Umeå Interdisciplinary Symposium on Hypoxic Biology. May 25th 2021.

Schedule

8.45. Felipe Cava and Emilio Bueno.

Introducing the symposium and Umeå Hypoxia Research Facility.

9:00. Michael Jetten. Radboud University (The Netherlands).

"Microbial conversion of ammonium and methane in oxygen-limited ecosystems by novel anaerobes"

9:40. Emilio Bueno. University of Umeå (Sweden).

"Hypoxic nitrate reduction in Vibrio cholerae divergently controls cell growth in response to varying environmental pHs"

10:00. Francesco Licausi. University of Oxford (UK).

"Turning blue in the green lineage: how plant sense and adapt to hypoxia"

10:40. Emily Flashman. University of Oxford (UK).

"N-Terminal Cysteine Dioxygenases: Oxygen-Sensing Enzymes in Plants"

11:20. Jonathan Gilthorpe. University of Umeå (Sweden).

"Hypoxia as a potential trigger for ALS"

Lunch

13:00. Randall Johnson. Karolinska institutet (Sweden).

"Hypoxia and the immune response".

13:40. Jane McKeating. University of Oxford (UK).

"Oxygen sensing and viral replication: implications for tropism and pathogenesis"

14:20. Robert A Cramer. Geisel School of Medicine at Dartmouth (US).

"Hypoxia Mediated Disease Progression and Drug Resistance in the Human Pathogen Aspergillus fumigatus"

15:00. Constantin Urban. University of Umeå (Sweden).

"Fungal adaption to hypoxia drives virulence"

Break 20min

15:40. Björn Schröder. University of Umeå (Sweden).

"Interaction between the gut microbiota and the intestinal mucosal barrier"

16:00. Andreas Baumler. UCDAVIS (US).

"Healthy guts exclude oxygen"

1st Umeå Interdisciplinary Symposium on Hypoxic Biology. May 25th 2021.

Oral presentations Abstracts.

8.45. Felipe Cava and Emilio Bueno. Introducing the symposium and Umeå Hypoxia Research Facility.

9:00. Michael Jetten. Radboud University (The Netherlands).

"Microbial conversion of ammonium and methane in oxygen-limited ecosystems by novel anaerobes"

During the evolutionary history of our planet, a set of microbial processes that evolved exclusively in the absence of oxygen changed the chemical speciation of all major elements. In the past 20y we aimed to discover and elucidate the role of these anaerobic microbes in the nitrogen and methane cycles. Molecular studies showed that anammox bacteria occur in many oxygen-limited ecosystems, and that they can make the rocket fuel hydrazine by novel protein complexes that are located in a unique bacterial organelle. Anaerobic oxidation of methane by *Methanoperedens* archaea and *Methylomirabilis. oxyfera* bacteria have recently been discovered. M. oxyfera bacteria turned out to have a new intra-aerobic metabolism. They are able to produce their own oxygen by conversion of 2NO into O_2 and N_2 by a putative NO dismutase. In addition to nitrate, *Methanoperedens* archaea can use metal-oxides as terminal electron acceptor. Furthermore, most if not all of these microorganisms can be applied in sustainable, cost effective oxygen-limited wastewater treatment for the removal of methane and nitrogen compounds, and are investigated within the center of excellence in anaerobic microbiology (www.anaerobic-microbiology.eu) funded by the Netherlands Gravitation program 024.002.002 SIAM and ERC Synergy MARIX.

9:40. Emilio Bueno. University of Umeå (Sweden).

"Hypoxic nitrate reduction in *Vibrio cholerae* divergently controls cell growth in response to varying environmental pHs"

During anaerobiosis, many bacteria depend on NO_3^- to enable respiration and optimal growth; this process involves sequential reduction reactions, beginning with the nitrate-reductase mediated conversion of NO_3^- to NO_2^-, a toxic intermediate that must be further reduced by a nitrite- and nitric- reductases to avoid detrimental effects on the bacteria. The global pathogen *Vibrio cholerae* does not encode a nitrite reductase and is thought to accumulate toxic NO_2^- during growth. Moreover, prior reports claim that *V. cholerae* does not undergo NO_3^--dependent respiration. We employed a combination of high throughput genetics and metabolomics to investigate the metabolic regulation and physiological consequences of anaerobic NO_3^- reduction in *V. cholerae* survival/growth. We discovered that NO_2^- accumulation in *V. cholerae* and others enteropathogens serves an unexpected beneficial role by slowing population expansion and conserving cell viability in the face of rapid acidification during

fermentative growth. Conversely, *V. cholerae* can indeed undergo NO_3^- respiration, but that it does so selectively under alkaline conditions where NO_2^- toxicity is not as severe. These two pH-dependent phenotypes reveal a unifying molecular mechanism by which an organism can exploit a single redox reaction to divergently control growth outcomes in response to varying environmental states.

10:00. Francesco Licausi. University of Oxford (UK).

"Turning blue in the green lineage: how plant sense and adapt to hypoxia"

Although responsible for the oxygenation of our planet's atmosphere, plants also need oxygen for respiration. Hypoxia is experienced frequently by plant tissues, due to the steep oxygen gradients that are established by developmental programmes and limitations in oxygen availability from the surrounding environment, such as during flooding or soil waterlogging. Similar to animals, plants have developed an oxygen sensing system, based on selective proteolysis, to control transcriptional adaptation to hypoxia.

10:40. Emily Flashman. University of Oxford (UK).

"N-Terminal Cysteine Dioxygenases: Oxygen-Sensing Enzymes in Plants"

Plant Cysteine Oxidases (PCOs) are Fe-dependent thiol dioxygenases which catalyse the oxidation of N-terminal cysteine residues of target proteins, rendering them susceptible to degradation via the N-degron pathway. Primary targets of the PCOs are the Group VII Ethylene Response Factors (ERF-VIIs), transcription factors which direct adaptive responses to flooding. As flooding results in hypoxic conditions, PCO activity therefore directly connects O_2 availability and the physiological response. I will describe our work which has characterised PCO function, demonstrated that they are O_2 sensors and structural work which has revealed ways to manipulate PCO activity both *in vitro* and in plants.

11:20. Jonathan Gilthorpe. University of Umeå (Sweden).

"Hypoxia as a potential trigger for ALS"

Mutations in superoxide dismutase 1 (SOD1) cause the neurodegernative motor neuron disease, amyotrophic lateral sclerosis (ALS). Disease pathogenesis is linked to destabilization, disorder and aggregation of the SOD1 protein. However, the factors that trigger and promote this process are not understood. O2 is required for the correct folding of the SOD1 protein and we have used cultured human iPSCs-derived cell models to show that O2 is also a critical determinate of SOD1 stability. Our results provide the first evidence a mechanism by which non-genetic risk factors for ALS, such as ageing and conditions that reduce vascular perfusion, could promote the disease.

Lunch break

13:00. Randall Johnson. Karolinska institutet (Sweden).

"Hypoxia and the immune response"

Abstract: Hypoxic response is an essential aspect of immunity. I will present some of our data relating to this as well as discussing the synergies between different arms of the immune system as they relate to oxygen flux.

13:40. Jane McKeating. University of Oxford (UK).

"Oxygen sensing and viral replication: implications for tropism and pathogenesis"

Viral replication is shaped by the cellular microenvironment. One important environmental factor to consider is the local oxygen (O_2) tension, which can vary widely depending on the metabolic demand and blood supply of the tissue or organ. Whilst most *in vitro* studies on viral replication utilize cells cultured at atmospheric oxygen levels (approx. 18% O_2), the vast majority of human tissues have oxygen levels much lower than this (referred to as hypoxia). Hypoxia can have opposing effects on viral proliferation, inducing hepatitis B virus transcription (Wing 2021), whilst suppressing the infectivity of HIV (Zhuang 2020) and SARS-CoV-2 (Wing 2021). These contrasting effects are likely to reflect the variable oxygen tension at the sites of virus replication and the complex interplay between viruses and their hosts (Liu 2020).

14:20. Robert A Cramer. Geisel School of Medicine at Dartmouth (US).

"Hypoxia Mediated Disease Progression and Drug Resistance in the Human Pathogen *Aspergillus fumigatus"*

Infection microenvironments associated with diseases caused by the filamentous fungus *Aspergillus fumigatus* are in part characterized by reduced oxygen availability. The Cramer laboratory is exploring how these hypoxic microenvironments influence mechanisms of fungal mediated disease progression and resistance to contemporary antifungal therapies. In this seminar, recent data will be presented that illustrates the role of oxygen in fungal biofilm formation and architecture and its influence on both disease progression and the efficacy of contemporary antifungal therapies.

15:00. Constantin Urban. University of Umeå (Sweden).

"Fungal adaption to hypoxia drives virulence"

We investigate how the human fungal pathogen *Candida albicans* uses adaption to low oxygen levels in the gastrointestinal tract to evade immune attacks. Hypoxia triggers changes in cell surface composition of *C. albicans* which allow the pathogen to evade surveillance by neutrophils the most important immune cell in antifungal defense.

Break 20min

15:40. Björn Schröder. University of Umeå (Sweden).

“Interaction between the gut microbiota and the intestinal mucosal barrier”

The intestine is an anaerobic environment that is home to a complex community of microbes. As a protection against this microbial community, the intestinal epithelium produces antimicrobial peptides, which are host-produced peptide antibiotics. In our research we focus on the interaction between antimicrobial peptides and the gut microbiota.

16:00. Andreas Baumler. UCDAVIS (US).

“Healthy guts exclude oxygen”

An imbalance in the colonic microbiota might underlie many human diseases, but the mechanisms maintaining homeostasis remain elusive. Recent insights suggest that colonocyte metabolism functions as a control switch, mediating a shift between homeostatic and dysbiotic communities. During homeostasis, colonocyte metabolism is directed towards oxidative phosphorylation, resulting in high epithelial oxygen consumption. The consequent epithelial hypoxia helps maintain a microbial community dominated by obligate anaerobic bacteria, which provide benefit by converting fiber into fermentation products absorbed by the host. Conditions that alter the metabolism of the colonic epithelium increase epithelial oxygenation, thereby driving an expansion of facultative anaerobic bacteria, a hallmark of dysbiosis in the colon. Enteric pathogens subvert colonocyte metabolism to escape niche protection conferred by the gut microbiota. The reverse strategy, a metabolic reprogramming to restore colonocyte hypoxia, represents a promising new therapeutic approach for rebalancing the colonic microbiota in a broad spectrum of human diseases.

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