Session 18: Regulation of cell metabolism

Lectures

L.18.1

Harnessing the microbiome to improve human health

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The gut microbiota is a collection of microbes, which inhabit our intestines. It is becoming apparent that the interactions between these microorganisms and human cells are central to maintaining health and become dysregulated in disease. Despite this, one question remains unanswered: how does the gut microbiota influence immune function in distal body organs, such as the brain and lungs?
In recent years, we and others have gained important advances towards unravelling the mechanisms that underline the "gut-lung axis" and "gut-brain axis" as we pointed to the presence of gut-derived metabolites in these organs. Following up on this, we identified a microbial metabolite, which inhibited inflammatory responses in cells from these areas. In lung cells, it inhibited the production of cytokines and chemokines characteristic of acute respiratory distress syndrome (IL-6, CXCL1 or CXCL10). In glia, it ameliorated the production of mediators typically upregulated in multiple sclerosis patients (IL-6, CCL2 or CCL20).
In this talk, I will discuss our approach to harness the potential of microbial metabolites to improve human health.

L.18.2

Breathing with confidence: Interplay between Immunity and Metabolism in Asthma and COVID-19

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Rhinoviruses (RV) and allergens, such as house dust mite (HDM) are major agents responsible for asthma exacerbations. The influence of airway inflammation on the infection with SARS-CoV-2 is controversial. We study mechanisms of response to viral infection in experimental in vivo infection in healthy controls and patients with asthma, and in vitro in human primary airway epithelium. RV infection in patients with asthma leads to an excessive RIG-I inflammasome activation, which diminishes its accessibility for type I/III interferon responses, leading to their early impairment, delayed resolution, prolonged viral clearance and unresolved inflammation. Pre-exposure to HDM augments this phenomenon by inflammasome priming and inhibition of early type I/III interferons. Prior infection with RV followed by SARS-CoV-2 infection augments RIG-I inflammasome activation and epithelial inflammation. Uncoupling of RIG-I from its canonical type I/III INF pathway is controlled by metabolic reprogramming, enhanced by HDM exposure. IL-13, the main type 2 cytokine, decreases expression of long ACE2 mRNA and reduces glycosylation of full-length ACE2 protein *via* alteration of N-linked glycosylation process, limiting its availability on the apical side of ciliated cells. This process is also partially regulated by metabolic reprogramming. Rhinovirus infection increases short ACE2 mRNA, but it does not influence its protein expression.

L.18.3

Impact of ubiquitin-dependent signaling events on the regulation of adipose tissue function

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The ubiquitin pathway is implicated in almost every cellular pathway described. However, little is known about the importance of ubiquitin in the regulation of metabolism in adipose tissue. Adipocytes acquire a unique morphology, consisting of a lipid droplet occupying the majority of the intracellular region. The major function of brown adipocytes is to dissipate energy in the form of heat. The main function of white adipocytes is to store energy as triglycerides (TGs) when energy is available in excess. Upon food deprivation, TGs stored in lipid droplets are degraded in the process of lipolysis. Adrenaline acting via β-adrenergic receptors is the major factor promoting the catabolism of TGs.
To investigate the global changes in ubiquitination of proteome of brown and white adipocytes, two new adipocytic cell lines brown and white, T37i and 3T3L1 inducible expressing 6His-ubiquitin respectively were generated. After the differentiation of both cell lines, ubiquitinated proteins were enriched by immunoprecipitation and analyzed by mass spectrometry (MS). Interestingly, our results indicate that among other ubiquitinated proteins identically expressed in both cell lines, some E3 ubiquitin-ligases were detected in the top hits of brown adipocytes. We focused on these ubiquitin ligases to answer how this specific players will impact the regulation of brown adipose tissue functions.

L.18.4

Investigating the oral microbiome changes during chemotherapy in breast cancer patients

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Oral microbiome is composed of more than 700 species of bacteria being the second largest microbial community in our organism after the gut [1]. The composition of the "normal" microbiome has been described and defined through the years [2–4]. Oral microbiome has been associated with various diseases, including breast cancers [7]. Cancer therapy-induced oral mucositis (CTOM) in patients treated with chemotherapy [8] may also be associated with the oral microbiome status.
The goal of the presented pilot project is to discover an influence of chemotherapy on the oral microbiome status and oral mucositis, and to further identify bacterial groups involved in the inflamatory processes affecting oral cavity.
In the our study, we investigate the oral microbiome changes during chemotherapy in breast cancer patients. We recruited 20 women diagnosed with triple negative or HER2 negative subtypes of breast cancer and assigned to the same AC chemotherapy scheme. Using 16S RNA sequencing with Nanopore technology we sequenced salivary microbiome in three time points of the chemotherapy: before the first dose, 2 weeks after the first dose and after the 4th dose.
Preliminary results (based on the partial data) indicate the presence of 13 to 19 dominating bacterial genera in saliva samples of breast cancer patients and no significant changes in genera diversity in the course of chemotherapy. The chemotherapy caused changes of genera abundances require more data and further investigation.