OR Imunologie

Vypsané doktorské práce pro akademický rok 2020/2021 pro II kolo přijímacího řízení

The role of immune metabolism in the control of NK cell cytotoxicity.

Mgr. Jan Frič, Ph.D.

ID 231791

The metabolic processes and energy sources are key factors necessary for an effective immune response. There is a growing body of evidence that cell metabolism is integral to immune cell effector functions. The project is therefore focused on study of energy metabolism of immune cells, that can be used for cell immunotherapy, especially NK cells and gamma-delta T lymphocytes. The aim is to determine and understand molecular mechanisms responsible for the changes in cell metabolism and their linkage to immune response and cell cytotoxicity. The cytotoxic cells used for immunotherapy prosper in optimal conditions of cell culture with abundance of nutrients and growth factors. The adoptive transfer to bloodstream of patient is a significant change of cells microenvironment. The aim of this study is to examine the direct link between the cytotoxicity of immune cells and the alteration of external environment, where cells can be exposed to lack of nutrients, hypoxia, metabolites or pro-inflammatory cytokines, in common factors that can significantly affect their immunometabolism and/or decrease their cytotoxic activity. Various cellular and molecular immunology methods will be used to prepare the doctoral thesis including flow cytometry, Seahorse analysis, Western blot, ELISA. Overall the project will contribute to better understanding of processes and mechanisms controlling effector cytotoxic function of immune cells participating in the immunotherapy of haemato-oncological diseases.

Leukocyte motility and migratory behaviour.

Mgr. Miroslav Hons, Ph.D.

ID 223911

An efficient immune response requires cells of the immune system to be at the right place at the right time and depends on their migration and correct positioning in tissues. Our research team examines mechanisms which enable immune cells to establish motile behavior and we explore how defects in leukocyte motility impact immunity on the system level.

Locomotion of leukocytes is driven by molecules distributed in the environment such as chemokines or molecules from damaged cells or bacteria. Those chemical signals are recognized by specific receptors on the surface of leukocytes and trigger signaling cascades resulting in rapid reorganization of cytoskeleton, morphological changes and motility. Nevertheless, leukocytes migrate in tissues with diverse physical properties. Some tissues might be porous but others can be dense and difficult to crawl through. Tissues are also often inhomogeneous and migrating leukocytes have to be able to avoid physical obstacles to find their way. Thus, leukocytes must be able to read two kinds of signals: chemical - coming out of biologically active molecules, and mechanical - from surrounding tissues. We focus on how leukocytes recognize mechanical inputs and what mechano-receptors they use. We also want to understand how leukocytes integrate mechanical and chemical signals and how mechanical stress influences leukocytes behavior.

We use live cell imaging to record and analyze leukocytes behavior and their morphological and cytoskeletal dynamics. To expose cells to mechanical stress under experimental conditions we manufacture custom-made devices that can be used to expose cells to mechanical confinement or they can be imprinted with microchannels that can form various constrictive geometries. To complement this reductionistic approach, we study migratory behavior of leukocytes in lymphoid organs and peripheral tissues with intravital imaging.

We are looking for motivated candidates interested in cell biology, cytoskeleton, immunology and microscopy. We seek for candidates with various backgrounds and applicants without previous experience with related topics are encouraged to apply.

We offer:

- Opportunity to work in a newly-established team within a multidisciplinary institution.
- State-of-the-art infrastructure.
- Part-time position.

For more insight please see:

https://www.biocev.eu/en/research-program/cellular-biology-and-virology.4/leukocyte-motility.66

https://www.biocev.eu/en/career/scientific-and-study-positions/phd-student-position-leukocyte-motility-lab.102

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The impact of early postnatal probiotic and antibiotic administration on interaction between microbiota and host immune system in health and disease

doc. RNDr. Jiří Hrdý, Ph.D.

ID 230632

With increasing incidence of allergic and inflammatory bowel diseases (IBD) there is a growing need for the identification of early prognostic markers pointing to increased risk of allergy and IBD development and early preventive measure introduction. Recently, the impact of microbiota on host immune responses has been acknowledged. Dysbiosis (changes in microbiota composition and function) could facilitate development of immunopathological responses leading to origination of disorders (e.g. inflammatory bowel diseases, autoimmune diseases, allergic diseases etc.). Probiotic supplementation seems to be a suitable and easily feasible preventive measure correcting for the dysbiosis. Importantly, the effect of probiotics is highly strain dependent. In our previous studies, probiotic strain of Escherichia coli O83:K24:H31 (EcO83) administered to newborns within 48 hours after delivery decreased allergy incidence in EcO83 supplemented children in comparison to non-colonized children 6, 8, 10 and 20 years after primary EcO83 administration (Hrdý et al., 2016, 2018, Lodinová-Žádníková et al., 2003). It seems that early postnatal EcO83 administration contributes to maturation of neonatal immune system (promoting Th1 and setting immunoregulatory responses, Súkeníková et al., 2017; Hrdý et al., 2018). Nevertheless, detailed understanding of beneficial mechanisms of EcO83 is necessary for effective preventive measure. The main aim of the project is the contribution to the understanding of the mechanisms of interaction between host immune system and microbiota. How eventual dysbiosis caused by antibiotic usage (ATB) affects homeostatic immune responses and how dysbiosis contributes to the development of immunopathological states (inflammatory bowel diseases, allergy). The impact of early postnatal EcO83 administration on maturation of neonatal immune system and setting homeostasis between developing microbiota and host immune system will be tested in experimental mouse models. Also, we will focus on the clarification of mechanisms how probiotic strain of E. coli O83:K24:H31 contributes to the normalisation of gut microbiota composition after ATB and setting new homeostatic interactions between microbiota and host immune system in health and disease. The preventive effect of EcO83 on allergy and IBD development will be tested using experimental mouse allergy models and TNBS induced acute colitis (Hrdý et al., 2020), respectively.

The role of microbiota components and their metabolites in mouse gnotobiotic model of human diseases

Ing. Tomáš Hudcovic, Ph.D.

ID 231492

The composition of the intestinal microbiota is a key factor that is responsible for the maturation of the immune system and thus for the health of the host. If the bacterial balance of the intestinal microbial communities is disturbed, so-called dysbiosis occurs. Taxonomic diversity of microbial communities has been shown to be lost in patients with inflammatory bowel disease (IBD).

Ulcerative colitis (UC) belongs to chronic idiopathic inflammatory bowel diseases. A suitable experimental animal model that develops intestinal inflammation similar to UC is dextran sodium sulfate model. The effect of identified bacteria of patients with UC on the pathogenesis of inflammation will be studied in a mouse gnotobiotic model (germ-free mice, targeted monocolonized mice, conventional controls and IL-10 deficient mice). In these experimental models we will also determine the effects of bacteria with protective probiotic effects - Escherichia coli Nissle 1917 and Clostridium (C.) tyrobutyricum. In the bacterium C. tyrobutyricum, we will also focus on evaluating the effect of butyrate and other produced metabolites on the pathogenesis of inflammation.

The doctoral student will study the in vitro immunomodulatory properties of bacteria using HEK cells stably transfected with innate immune receptors, human THP-1 line, mouse RAW line and mouse bone marrow derived dendritic cells. The influence of bacteria on innate and adaptive immunity development in the UC model will be evaluated histologically, immunohistochemically, by determining proinflammatory and anti-inflammatory cytokines by ELISA and their mRNA, mRNA to evaluate mucin production (MUC2) and the presence of tight junction proteins. Toll-like receptor expression will be monitored at the mRNA level by RT PCR and at the protein product level by Western blotting. The cell subpopulations will be evaluated by flow cytometry. Mass spectrometry will be used for qualitative and quantitative analysis of metabolites.

Gut microbiota role in development of chronic diseases

Mgr. Klára Kostovčíková, Ph.D.

ID 231624

Gut microbiota has significant role in the pathogenesis of numerous metabolic, autoimmune and neoplastic diseases. As a source of various antigens and metabolites, microbiota can influence gut barrier function and mucosal and systemic immune response. Recent studies have highlighted its possible effects on epigenetic changes in the pathogenesis of chronic diseases, such as inflammatory bowel diseases (IBD) and colorectal cancer.

Main goal of the thesis will be to describe epigenetic modifications associated with gut inflammation and tumor development in patients with chronic diseases and in mouse models of IBD and colorectal cancer. For this purpose, mouse microbiome will be experimentally modified, e.g. by diet or antimicrobials, before disease induction. Immuno-modulatory mechanisms of certain microbes or their metabolites will be tested in vitro on primary cells and cell lines. The student will use immunological techniques (e.g. ELISA, flow cytometry, immunofluorescence) and methods of molecular-biology (e.g. RT-PCR, sequencing) to fulfill the goals.

Myokines and metabolically active molecules in the pathogenesis of idiopathic inflammatory myopathies

prof. MUDr. Jiří Vencovský, DrSc.

ID 231950

Patients with idiopathic inflammatory myopathies (IIM) suffer from muscle weakness and muscle wasting, a condition in which increased pro-atrophic and decreased anabolic factors, such as myokines myostatin and follistatin, would be expected. However, our recent data showed reduced circulating myostatin accompanied by attenuation of its signalling in chronic IIM patients compared to healthy individuals. IIM patients struggle with the reduced ability to carry out daily physical activities, including walking. Thus, the complex IIM pathogenesis is further potentiated by limited

contractile activity and muscle disuse, which promote muscle atrophy, lipid accumulation and mitochondrial dysfunction.
The aim of the presented project is to investigate, whether the observed myostatin and metabolic dysregulation drives the pathogenesis of IIM or it is a consequence of autoimmunity-related process. To answer that, newly diagnosed patients at the onset of the disease and 6 months after pharmacotherapy will be analysed. In addition, the results between patients well- and weakly-responding to the therapy will be compared. Myokines, muscle atrophy- and muscle growth-related proteins will be analysed in sera as well as in muscle tissue of IIM patients and related to disease progression, response to therapy and daily physical activity. PhD student will be involved in all aspects of the research work such as patient recruitment, laboratory work (serological analyses, primary muscle cell cultures, gene and protein expression, fluorescent microscopy), data analysis and manuscript drafting. The project refers to a submitted grant application MZČR NU21-05-00322.