Laboratory of Immunobiology

Innate immune receptors, neutrophils, defensins, TCR signalling

Dominik Filipp

dominik.filipp@img.cas.cz

The group was established in the summer of 2007. The central theme of our research is the molecular and functional characterization of innate immune mechanisms involved in the process of sterile inflammation, developmental tissue remodelling and chronic inflammatory diseases. Our main effort is focused on Toll-like receptors and other TIR domain-containing immune-related proteins and their role in the early embryogenesis. Data accumulated so far point to the spatially and temporarily regulated expression of TLRs on embryonal phagocytes, suggesting their involvement in sterile inflammation during early development. The characterization of a complete set of innate immune receptors (IIRs) expressed on embryonal phagocytes and evaluation of their signalling competence, together with elucidation of the nature of endogenous ligands for these IIRs represent our main objectives. Further, the cDNA microarray analyses performed on embryonal phagocytes revealed cell-specific expression of several uncharacterized molecules that could play an essential role in the processes supporting embryonal homeostasis. In collaboration with our partner laboratories we have also characterized immunomodulatory activities of enzymatically synthesized oligofuranosides (1). Recent data indicate their robust adjuvant properties with prophylactic and therapeutic potential. Our research is also geared towards the understanding of the contribution of cellular and humoral innate immune factors to the onset and maintenance of autoimmune processes. In collaboration with clinical laboratories we were able to demonstrate increased levels of defensin expression in recently diagnosed patients suffering from autoimmune diseases. Our main mission here is to characterize novel predictive biomarkers suitable for diagnosis of these diseases in the pre-clinical phase of their development. In this context we have also characterized the distribution and tissue-specific functions of alpha-defensins in rat experimental models (2). We also continue in our effort to understand very early biochemical events leading to activation of T cells. Our previous study showed that the critical event in this process is the translocation and subsequent enrichment of kinase active Lck in lipid rafts (LR) (3). While other regulatory proteins are also recruited to LR upon T-cell activation, the mechanism of these translocations, indispensable for T-cell activation, is largely unknown. The main goal of this line of research is the characterization of the molecular mechanism and its structural elements underpinning the recruitment of Lck and other signalling molecules to LR. In addition, we provide technical and knowledge support for exploration of several molecular approaches in unrelated projects (4, 5).

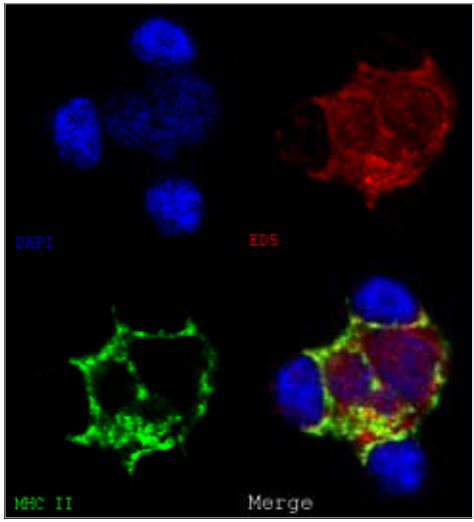

Fig. 2. Medullar thymic epithelial cells (mTECs) of Wistar rat produce enteric defensin ED5. Imunofluorescent confocal microscopy revealed multiple cellular interactions between mTEC and thymocytes.

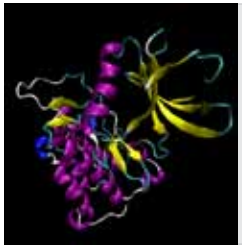

Fig. 1. Using a combination of biochemical, genetic and computer modelling approaches provides new insights into the regulation of Lck activity (image by V. Spiwok, MSc, ICT, Prague).

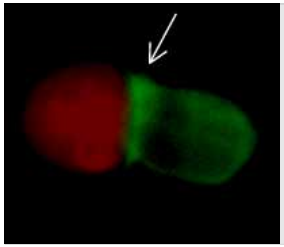

Fig. 3. Newly identified adaptor protein (green) co-redistribute with Lck into forming immunological synapse (arrow) during early phases of $CD4^+$ T-cell/APC interaction.

- AS CR, IAA500520707 – The role of innate immune molecules in embryonic homeostasis and sterile inflammation, 2007-2011, D. Filipp
- Ministry of Education, Youth and Sports of the Czech Republic, 2B08066 – Novel treatment of genetically determined metabolic disease, type 1 diabetes, using an immunotherapeutical approach, 2008-2011, D. Filipp
- Ministry of Defence of the Czech Republic, OVUOFVZ200808 - Development of new prophylactic tools against Francisella tularensis infection, 2008-2011, D. Filipp
- GA CR, GA310/09/2084 – Characterization of the molecular machinery regulating the recruitment of signalling molecules to lipid rafts, 2009-2013, D. Filipp

1. Chlubnová I, Filipp D, Spiwok V, Dvořáková H, Daniellou R, Nugier-Chauvin C, Králová B, Ferrieres V. Enzymatic synthesis of oligo-D-galactofuranosides and L-arabinofuranosides: from molecular dynamics to immunological assays. **Org Biomol Chem 2010** 8(9): 2092-2102.
2. Neuwirth A, Dobeš J, Cmarko D, Selsted ME, Filipp D. Unexpected complexity of alpha-defensin expression in the rat thymus (submitted).
3. Filipp D, Moemeni B, Ferzoco A, Kathirkamathamby K, Zhang J, Ballek O, Davidson D, Veillette A, Julius M. Lck-dependent Fyn activation requires C terminus-dependent targeting of kinase-active Lck to lipid rafts. **J Biol Chem 2008** 283(39): 26409-26422.
4. Jirsova K, Neuwirth A, Kalasova S, Vesela V, Merjava S. Mesothelial proteins are expressed in the human cornea. **Exp Eye Res 2010** 91(5): 623-629.
5. Merjavá S, Neuwirth A, Tanzerová M, Jirsová K. The spectrum of cytokeratins expressed in the adult human cornea, limbus and perilimbal conjunctiva. **Histol Histopathol 2011** 26(3): 323-331.

From left:
Dominik Filipp, PhD / Head of Laboratory
Jan Dobeš / Diploma Student
Zdeňka Hanusová / Diploma Student (since 2010)
Jana Gujezdská, MSc / PhD Student
Tereza Vavrochová, MSc / PhD Student (since 2010)
Ondřej Ballek, MSc / PhD Student (since 2009)
Aleš Neuwirth, MSc / Research Assistant

Not on the picture:
Martina Benešová / Technician (since 2010)
Adéla Broučková, MSc / Research Assistant (until 2010)
Anežka Fišerová, MD / Research Assistant (until 2009)
Jana Jelínková, PhD / Research Fellow (maternity leave)
Jan Valečka / Diploma Student (since 2009)