Doc. MUDr. Radek Špíšek, Ph.D.
Ústav imunologie, UK 2.LF
V Úvalu 84
150 06, Praha 5
224 435 963
radek.spisek@lfmotol.cuni.cz

Praha, 1.10.201

Review of the PhD thesis: Studies on immunoreceptor signaling molecules

In her PhD thesis Tereza Ormsby summarizes the experimental data from three independent studies that focus on different aspects of intracellular signaling in leukocytes. Structure of the thesis is logical, well written and is easy to read. In the introduction author concentrates only on the aspects relevant for the experimental part and yet it´s easy to follow the reasoning and hypothesis that initiated the research. Second part of the thesis is composed of three original articles published in respected scientific journals that result from the cooperation between the laboratories of V.Horejsi (Prague) and A. Cerwenka (Heidelberg). T. Ormsby coauthored two of them, in the International Journal of Cancer and Journal of Biological Chemistry, and is the first author of the recent paper published in The Blood journal.

Study in the International journal of Cancer describes the upregulation of ICAM 1 in human keratinocytes after transduction with HPV16. Expression of ICAM 1 enhanced the NK cell mediated killing of cervical carcinoma cell line.

Paper in the Journal of Biological Chemistry studies the role of PRR7 transmembrane adaptor protein in resting and activated T cells.

In the paper in Blood, authors studied the role of Btk in myeloid cells and describe a novel role of Btk in TREM-1 signaling pathway as a positive regulator of proinflammatory cytokines production.

I have the following questions complementing the published reports:

- Regarding the expression of ICAM-1 after the transduction with HPV: do the transduced cells express other markers that could indicate their increased immunogenicity? Do the transduced cells also activate antigen specific T cells?
- The role of Btk in B cells results in X linked agammaglobulinemia and is well described. There is now a considerable interest to understand its role in myeloid cells. There is a number of contradictory studies on the impact of Btk deficiency in myeloid cells that are nicely reviewed in the Introduction section. Some reports indicate that Btk associates with the TIR domain of TLRs 4,6, 8 and 9 and other components of TLRs signaling pathway. Could you please reconcile this finding with your finding of Btk being phosphorylated after TREM-1 ligation?

- Based on your expertise, what defects of myeloid cells would you expect in XLA patients and how this fits in the published studies?

During her PhD studies T.Ormsby showed a proficiency in the vast number of methods as documented by three original articles in the first tier scientific papers. The results of her scientific projects clearly show that she meets the requirements set by the Immunology board of PhD studies and she can be awarded the PhD degree.

Radek Špíšek