Abstract

A delicate balance in the number, specific type and function of leukocytes is required for proper functionality of the mammalian immune system. Innate immunity, which quickly recognizes pathogens, represents the first line of defense. Later, a more specific response is generated via adaptive immunity. Deregulation of the immune system is manifested by the inability to control infection, development of allergic, autoimmune disorders or even cancer, and ultimately can lead to death. To fulfill their functions, cells develop an intricate network of intra- as well as extra-cellular molecules organized into signaling cascades, which allows them to communicate between each other. Better understanding of the molecular mechanisms of signaling pathways in leukocytes is critical for design of efficient therapies.

In this thesis, leukocyte signaling was studied in several aspects. First, the role of adhesion molecules in pathogenesis of cervical cancer and the regulation of their expression was investigated. The second publication describes a new transmembrane adaptor protein (TRAP), called prolin rich 7 (PRR7), as a potentially interesting regulator of signaling and apoptosis in activated T cells. The final publication characterized the role of the Btk kinase downstream of the triggering receptor expressed on myeloid cells 1 (TREM-1), which was shown to be involved in inflammatory processes; suppression of its activity had beneficial effects in the treatment of septic shock.

This thesis is based on three publications:

1. Textor S., Accardi R., **Havlová T.**, Hussain I., Sylla B.S., Gissmann L., Cerwenka A. 2010. NF-κB-dependent upregulation of ICAM-1 by HPV16-E6/E7 facilitates NK cell/target cell interaction, *Int J Cancer* 128: 1104-1113

2. Hrdinka M., Dráber P., Štepánek O., **Ormsby T.**, Otáhal P., Angelisová P., Brdička T., Pačes J., Hořejší V., Drbal K. 2011. PRR7 is a transmembrane adaptor protein expressed in activated T cells involved in regulation of T cell receptor (TCR) signaling and apoptosis, *J Biol Chem* 286: 19617-29

3. **Ormsby T.**, Schlecker E., Ferdin J., Tessarz A.S., Angelisová P., Köprülü A.D., Borte M., Warnatz K., Schulze I, Ellmeier W., Hořejší V., Cerwenka A. 2011. Btk is a positive regulator in the TREM-1/DAP12 signaling pathway, Blood [ahead of print, doi:10.1182/blood-2010-11-317016]