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Innate immune receptors and their signalling, sterile inflammation, TCR signalling

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Research topics

Our newly formed group became functional 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 the identification of their putative endogenous, self-derived ligands. Data accumulated so far point to spatially and temporarily regulated expression of TLRs on embryonal phagocytes, suggesting their involvement in sterile inflammation during early development. The characterization of the complete set of innate immune receptors (IIRs) expressed on embryonal phagocytes and evaluation of their signaling 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 a cell-specific expression of several uncharacterized molecules that could play an essential role in the processes supporting embryonal homeostasis. The insight gained from genetic, biochemical and microscopic approaches (Figs. 1 and 2) will contribute to our understanding of the process of sterile inflammation and its role in embryonal development.

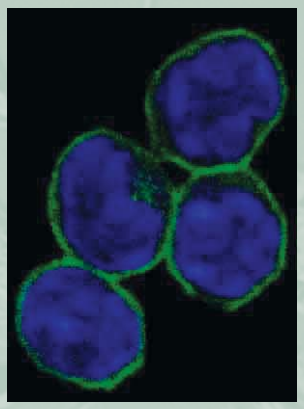

Fig. 1. Fluorescent microscopy of the primary CD4⁺ T cells stained with DAPI (blue, nuclei) and anti-Lck (green). Activation and subsequent translocation of membrane-associated Lck to lipid rafts predicates T-cell activation (see the paper and references in it).

Other researchers in our group study early events leading to activation of two Src-family tyrosine kinases (SFK) Lck and Fyn during the initiation of membrane proximal T-cell signalling. The essential event in this process is the translocation and subsequent enrichment of kinase active Lck in lipid rafts (LR) (Fig. 1). 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. In this context, we have identified the previously uncharacterized role of the C-terminal sequence of Lck (YQPQP) in its targeting to LR (ref. 1). The main goal of this line of research is the characterization of the molecular mechanism underpinning the recruitment of Lck and other signalling molecules to LR.

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Selected recent papers

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;283:26409-26422.

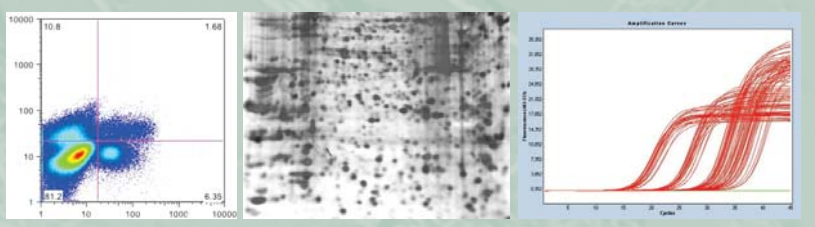

Fig. 2. FACS analysis, 2-D gel electrophoresis, 384-multiwell qRT-PCR and immunofluorescent confocal microscopy (Fig. 1) belong to a standard battery of techniques used in the laboratory to analyse the cells and molecules of immune system.