Abstract

The ERK signalling cascade belongs to a familly of the signalling pathways conserved in eukaryotic cells, which responds to the wide spectrum of extracellular stimuli and convert these stimuli to appropriate response. In epithelial cells the ERK signalling cascade induces disintegration of epithelial architecture and induces morphological changes leading to the gain of the autonomy of the epithelial cells. During morphological changes of the epithelial structure, the ERK signalling cascade participates in the remodelling of the actin cytoskeleton, which leads to the disassembly of cell-cell adhesions and the loss of the epithelial polarity. Subsequently ERK activates the migration programme, which enables epithelial cells to use individual mesenchymal-like mode of migration. The so called peripheral actin is one of the least explored actin structures that forms at the periphery of the epithelial cells and surrounds the colony of epithelial cells. Peripheral actin is located at the basal side of the cell and it probably takes part in the integrity of epithelial tissue. Nevertheless, up to date it is not know if and how ERK signalling cascade regulatesthe peripheral actin and if remodeling of peripheral actin takes part in the cell migration.

In this thesis we show, that ERK signalling cascade is important for the remodeling of peripheral actin. The Activation of the ERK signalling cascade leads to the disintegration of this actin structure that is substituted by the dendritic actin of lamellipodia. This sequence of events alows cells to establish the mesenchymal mode of migration resulting in scattering of epithelial colonies. In addition, we found that protein kinase ERK2 is the preferred ERK isoform participating in the process of remodelling of the peripheral actin. Protein kinase ERK2 use its DBP-domain for remodelling of peripheral actin suggesting that the interaction of ERK2 with the substrate containing aminoacids motif Phe-Xxx-Phe is necessary for peripheral actin remodeling. This finding enabled us to identify possible ERK substrates which are necessary for the peripheral actin remodeling.

Key words: ERK, CD-domain, DBP-domain, actin, calpain, Rho-GTPases