Summary of the Thesis

„Molecular function of cortactin in signal transduction and pathogenesis of gastric epithelial cells “

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Cortactin is a multifunctional protein involved in many signaling processes of eukaryotic cells. Since its discovery as an actin-binding protein and substrate of Src kinase in the early 1990’s, cortactin has emerged as a key signaling protein in many cellular processes, including cell adhesion, migration, endocytosis, tumor invasion, morphogenesis and microbial infections. While the list of cellular functions influenced by cortactin grows, very little is known about the regulation of the protein at the molecular level. Aim of this project was to investigate the molecular function of cortactin in AGS gastric epithelial cells as *in vitro* infection model system. The results of this work show that cortactin’s function is regulated by two separate kinase signaling pathways including the phosphorylation/dephosphorylation of cortactin at three distinct serine and tyrosine residues, respectively. Depending on the phosphorylation status, cortactin changes both its subcellular localization and its ability to bind and activate downstream signaling factors. Upon infection, two novel interaction partners of cortactin were identified in this study - focal adhesion kinase (FAK) and a guanine exchange factor (Vav2). The respective protein/protein-interactions, downstream signaling as well as phenotypical changes were investigated in detail. The following five major results were obtained in my thesis: (1) Cortactin can be phosphorylated by two serine-/threonine kinases (Erk and Pak) at three distinct serine residues (S-113, S-405 und S-418); (2) Serine-phosphorylated cortactin interacts using its SH3 domain with a novel proline-rich sequence in FAK, called PR3, which profoundly stimulates the kinase activity of FAK; (3) Cortactin undergoes dephosphorylation at two tyrosine residues (Y-421 and Y-482) during infection, while another tyrosine residue (Y-466) is stabilized in its phosphorylation level; (4) Phosphorylated cortactin at tyrosine 466 interacts with the SH2 domain of Vav2 and activates the small Rho GTPase Rac1; and (5) the Cortactin/Vav2/Rac1-complex induces the dissociation of cell-to-cell contacts and enhances cell migration, all of which are processes known to play important roles in tumor progression and metastasis. Thus, the results of this study not only have important impact on our current understanding of cortactin’s function and regulation at the molecular level but may also give important new hints to develop novel therapeutic schemes for treatment of certain human diseases where cortactin is involved.