Abstract and keywords:

During metastasis, cancer cells can invade the extracellular matrix using various strategies. When invading individually, they employ either the amoeboid invasion mode, during which the cell body dynamically deforms by enhanced contractility to squeeze through pores within the matrix, or protease dependent mesenchymal migration that takes advantage of the possibility to digest the surrounding matrix. Cells migrating in one mode can actively switch to the other by mesenchymal-amoeboid (MAT) or amoeboid-mesenchymal transitions (AMT). This enables escape mechanisms and considerably complicates anti-metastatic treatment. It is well known that Rho GTPases are master regulators of cytoskeleton re-arrangements and thus, unsurprisingly, play a major role in both invasion modes and can directly drive the transitions. However, upstream activation of these pathways is still largely unclear. This thesis aimed to optimize 3D conditions suitable for studying plasticity of cell invasion *in vitro*, establish AMT and MAT in melanoma cells based on manipulation of Rho GTPases and verify novel candidates regulating cell invasion plasticity based on previous RNA sequencing of cells before and after MAT. Last, by synthesis of published data, results from sequencing and new findings presented in this thesis, we propose that the amoeboid phenotype is established as a consequence of autocrine/paracrine signaling loops maintained by production of cytokines driven by RhoA-mediated inflammatory pathways- Jak/Stat and NFκB, which themselves converge on RhoA. Moreover, the relation to cancer stem cells and possible connection to *in vivo* amoeboid migration is discussed.

Key words: invasiveness, amoeboid, Rho GTPases, Jak/Stat, NFκB, MAT, AMT