SUMMARY

Tumour cell invasion is one of the most critical steps in malignant progression. It includes a broad spectrum of mechanisms, including both individual and collective cell migration, which enables them to spread towards adjacent tissue, and form new metastases. Understanding the mechanisms of cell spreading, and invasion, is crucial for effective anticancer therapy. Two modes of individual migration of tumour cells have been established in a three-dimensional environment. Mesenchymally migrating cells use proteases to cleave collagen bundles, and thus overcome the ECM barriers. Recently described protease-independent amoeboid mode of invasion has been discovered in studies of cancer cells with protease inhibitors.

During my PhD study, I have focused on determining the molecular mechanisms involved in amoeboid invasion of tumour cells. We have examined invasive abilities in non-metastatic K2 and highly metastatic A3 rat sarcoma cell lines. We have shown that even though highly metastatic A3 rat sarcoma cells are of mesenchymal origin, they have upregulated Rho/ROCK signalling pathway. Moreover, A3 cells generate actomyosin-based mechanical forces at their leading edges to physically squeeze through the collagen fibrils by adopting an amoeboid phenotype.

Amoeboid invasiveness is also less dependent on integrin adhesion to the extracellular matrix, and we have suggested the potential role of NG2 proteoglycan in amoeboid cell adhesion and invasion. We found that NG2 knockdown leads to decreased invasion, as well as reduced level of active Rho in both highly metastatic A3 rat sarcoma and A375M2 human melanoma cells. Conversely, overexpression of NG2 proteoglycan correlated with elevated Rho-GTP expression, and increased invasiveness of non-metastatic K2 rat sarcoma cells. Our findings strongly suggest the role of NG2 proteoglycan as an adhesive molecule involved in amoeboid invasion as well as its potential connection to the Rho/ROCK signalling pathway.

We have also compared invasive properties of G3-EM parental primary breast cancer cells and its derived neoplastic transformed G3S1 line. Our results have shown elevated cytoskeletal dynamics in more invasive G3S1 cells.