Abstract:

This thesis is focused on the epithelial mesenchymal interactions in tumors derived from squamous epithelium including tumors arising from minor cell population (melanocytes). This study is also reflecting aspects of epithelial glycobiology resp. the study of endogenous lectins, the galectins, in head and neck squamous carcinomas.

Galectins represent, in the current concepts of cell and tumor biology molecules with a remarkable potential. Galectins participate, besides in regulation of pre- and postnatal homeostasis in normal tissues, also in many pathological processes such as autoimmune reactions or malignancies. In this thesis, we demonstrated the presence of galectin-1 and -2 and their glycoligands in interphasic and mitotic nuclei, which may contribute to regulation of the cell cycle. Furthermore, we demonstrated galectin-9 as a sensitive marker of transformation normal to the dysplastic squamous epithelium in head and neck.

The epithelial mesenchymal interactions represent mechanisms, which are responsible for dynamic maintenance of the homeostasis of the organism during prenatal development, postnatal growth and during cyclic renewal of certain tissues. These interactions also participate in wound healing. On the other hand they play a crucial role in the process of tumor transformation, progression and metastasis. These interactions help to shape the specific microenvironment known in developmental and tumor biology as a *"niche"*. We showed the effect of tumor-associated fibroblasts on the induction of expression of the stem cell like markers in tumor cell line of hypopharyngeal carcinoma *in vitro*. Furthermore, we also compared the effect of cancer-associated fibroblasts from different tumor types on the breast ductal carcinoma cell line. We demonstrated in this experiment that the biological function of cancer-associated fibroblasts is almost uniform in this *in vitro* model regardless the type of source tumor.

In another set of proteomic experiments, we detected induction of expression of contractile cytoskeletal proteins in dermal fibroblasts under the influence of tumor cell line of hypopharyngeal carcinoma and so their possible conversion into myofibroblasts.

Novelty of this thesis is also in the application of the *in vitro* model to melanoma biology, where the cell interactions may also play a significant role. We demonstrated the effect of cancer-associated fibroblasts to induce expression of differentiation markers in tumor melanocytes and approximate their phenotype *in vitro* to phenotype observed *in vivo*. In consecutive study, we demonstrated the influence of tumor melanocytes on differentiation of keratinocytes in *in vitro* model. This effect is probably responsible for the pseudohyperplastic epithelium in the vicinity of melanoma. Using whole genome transcriptome analysis we

managed to determine growth factors such as FGF-2, VEGF and chemokines/cytokines like IL-8 and CXCL-1 responsible for this effect.

Epithelial mesenchymal interactions as well as the galectins play a crucial role in biology of tumor microenvironment. Understanding these mechanisms may contribute not only to the development of targeted and personalized oncology therapy of the tumors, but also improvement of surgery, which remains the key to successful treatment of the tumors.

Keywords: Epithelial mesenchymal interactions, stroma, cancer-associated fibroblasts, galectins, squamous cell carcinoma of the head and neck, melanoma.