Abstract

Therapeutic resistance of tumours represents an important clinical issue. We can classify the therapeutic tumour resistance in two ways. According to the clinical course, tumours can behave either as primary resistant, i.e. from the very beginning not responsive, or they can display a secondary (also called acquired) resistance, whereby an initial clinical response is lost and the tumour develops into chemo-, radio- or immunoresistant disease. An alternative classification distinguishes cell autonomous resistance mechanisms from resistance that relies on complex interactions within the context of tumour microenvironment. From the research perspective, modelling therapeutic resistance frequently involves experimental treatment of sensitive cancer cells and selection of daughter resistant cell lines. The Ph.D. thesis includes derivation of two unique models of urothelial bladder carcinoma therapeutic resistance.

The first model involves newly established urothelial carcinoma cell lines BC44 and BC44DoxoR, which resulted from a prolonged doxorubicin exposure of the mother cell line. The daughter chemoresistant cell line exhibits multidrug resistant phenotype, which extends beyond the selecting drug - doxorubicin - to four additional chemotherapeutic drugs (cisplatin, methotrexate, vinblastine, and gemcitabine). This cell autonomous multidrug resistant phenotype is associated with a significantly decreased proliferative activity and significantly lower mitochondrial metabolic capacity. Ultrastructurally, the BC44DoxoR cells show structures reminiscent of a special mitochondrial directed autophagic process, mitophagy, and we hypothesize that this could be related to the observed phenotypic changes.

Complex microenvironmental tumour processes involve in particular interactions between the very carcinoma cells and tumour stromal cells, like tumour fibroblasts or immune cells. During the establishment of the BC44 cell line, an extensive infiltration with mesenchymal cells has been noticed, which made us possible to establish, from the very same tumour, at the same time a fibroblastic stromal cell line as well - BC44Fibr. The BC44Fibr cells carry the normal diploid karyotype and they show an activated phenotype compatible with carcinoma-associated fibroblasts. An independent stromal cell model could be established based on bladder inflammatory myofibroblastic tumour cell line. Coculturing with carcinoma cell lines sensitive to certain treatment options yielded models of complex therapeutic resistance. BC44 in coculture with BC44Fibr showed a specific cisplatin resistance in a way that directly reflects interaction of both cell types. Stromal cells behave as quasi universal provider of therapeutic resistance to various sensitive urothelial carcinoma cell lines. As an example, the urothelial carcinoma cell line SW780, which is on its own sensitive to the immunomodulatory drug TRAIL, loses this sensitivity in coculture with BC44Fibr, and the immunosuppressive effects of the latter became evident in various additional analyses. At the same time, stromal cells activated a stem-like phenotype in cocultured carcinoma cells; cancer stem cells are viewed as an inherently resistant tumour cell subpopulation. Importantly, carcinoma cells exhibiting a strong positivity to various cancer stem cell markers localized to an immediate contact zone with stromal cells. Stromal cells are thus able to crucially contribute to preservation of stem-like resistant cells within the heterogeneous cancer cell population.