26

Remodelling the microenvironment of epithelial cancers to better understand cancer metastasis and drug effects

Christian Zoschke[1], Leonie Gronbach[1], Konrad Klinghammer[2], Ulrich Keilholz[3], Monika Schäfer-Korting[4]

[1]***Institute of Pharmacy (Pharmacology and Toxicology), Berlin, Germany***

[2]***Charié, Abteilung für Hämatologie und Onkologie, Abteilung für Hämatologie und Onkologie, Berlin, Germany***

[3]***Charité – Universitätsmedizin Berlin, Charité Comprehensive Cancer Center, Berlin, Germany***

[4]***Freie Universität Berlin, Institut für Pharmazie, Pharmakologie und Toxikologie, Berlin, Germany***

Purpose: Epithelial carcinomas like head and neck and non-melanoma skin cancer are among the most frequent cancers in man. Thereby, squamous cell carcinomas of the head and neck metastasize more frequently than their cutaneous counterparts, contributing to the high mortality. Recent studies in various cancer entities suggest the determining role of cancer microenvironment for the tumor's response to chemotherapy together with the challenges of intra-tumor heterogenicity (Stanta et al. 2018 Front Med, Ren et al. 2018 Mol Cancer). Herein, we emulate oral and cutaneous squamous cell carcinoma in stratified tumor microenvironment models and test drug efficacies. Moreover, we investigate the effects of confounders like body-site or the glycation of the extracellular matrix on epithelial differentiation.

Methods: Cancer cells, either from patient derived tumor tissue or cell lines, were grown together with normal primary keratinocytes and fibroblasts in an 3D *in vitro* model.

Results: Oral mucosa models with patient-derived cancer cells reliably preserved the tumor grading, while the cell lines reproducibly emulated one tumor grading. While three applications of 0.7 µg/mL docetaxel induced cell death and reduced proliferation, cetuximab (10 µg/mL or 100 µg/mL) failed to alter these parameters. Ingenol mebutate (150 µg/g) almost completely eradicated cancer cells from cutaneous cancer models following three applications of the commercial gel (Zoschke et al. 2016 J Control Rel).

The body site of which fibroblasts were isolated determined the epithelial differentiation in the respective skin constructs as shown for altered expression of e.g. granulocyte-macrophage colony-stimulating factor, e-cadherin, and filaggrin (Hausmann et al. in revision Sci Rep). Next, we replaced included a glycated extracellular matrix, being typical for aged or diabetic persons. These glycated constructs showed increased proliferation and differentiation in the epithelial layers (Rigon & Käßmeyer et al., in revision Int J Mol Sci).

Conclusion: In conclusion, stratified tumor microenvironment models closely mimic epithelial cancers *in vitro* and capture certain drug effects. However, fibroblasts and the extracellular matrix extensively modulate epithelial differentiation in these models. Emulating heterogeneous cancers in heterogeneous tumor microenvironments might improve the currently low predictive capacity of *in vitro* models for anti-cancer effects in patients.