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MAIN FIELDS OF RESEARCH; ABSTRACT

Radiotherapy is one of the most commonly used treatment modalities, alone or in combination with others. It induces a complex network of secreted factors that can stimulate tumor outgrowth, dissemination, incomplete tumor regression and immune reactions. Irradiation can contribute to tumor eradication by damaging cells, respectively their DNA, in such an amount which cannot be repaired anymore and will lead to mitotic catastrophe that either ends in senescence or death of the cell. Further, irradiation stimulates the activation of several signaling pathways. As part of an exhaustive IR dependent secretome analysis, which was previously performed in our laboratory, ADAM17 was identified to be activated in response to IR.

ADAM17 (a disintegrin and metalloprotease domain 17), also called TACE (tumor necrosis factor-α-converting enzyme), belongs to the ADAM protein family of disintegrins and metalloproteases. The most well-known function of ADAM 17 is to cleave the ectodomains of several transmembrane proteins. Usually, that cleavage occurs at the membrane-adjacent part of the molecule. Proteins with different functions can be processed by ADAM17-mediated ectodomain shedding: EGFR ligands, proinflammatory cytokines like TNFα, its receptor TNFRI and adhesion molecules. ADAM17 has in total over 70 different substrates to process.

After cleavage, the ligands can bind to their respective receptors on the same cell (autocrine effect), or they can bind to receptors on neighbouring cells. Alternatively, they can reach receptors on more distant cells in the same tissue (juxtacrine and paracrine effect), and even enter the bloodstream (endocrine effect). Therefore, we aim to mechanistically investigate the relevance of radiotherapy-induced ADAM17-activity and shed factors.

We have now genetically engineered human lung adenocarcinoma tumor cells with lentiviral-based doxocycline-inducible shRNA-constructs to efficiently downregulate ADAM17.
With this set-up we will be able to investigate the ADAM17-mediated paracrine and/or preconditioning effect *in vitro* and *in vivo*.
The project is highly relevant for translational cancer research, in particular for the field of lung adenocarcinoma and radiotherapy.

SPECIAL TECHNIQUES AND EQUIPMENT

Image-guided small animal irradiation (PXi), in vivo imaging system, clonogenic assay, nuclear repair foci staining, Western blotting