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MAIN FIELDS OF RESEARCH; ABSTRACT

Ionizing radiation (IR) leads to DNA damage and genome instability. In addition, IR also affects intra- and inter-cellular processes that induce a multilayered stress response and determines the tumor response to radiotherapy. As part of an IR-dependent secretome analysis, our laboratory demonstrated that direct targeting of the metalloprotease ADAM17 sensitizes lung carcinoma cells to radiotherapy.

Growth and survival of NSCLC cells are often dependent on ectodomain shedding which includes the proteolytic cleavage of the extracellular part of membrane proteins primarily mediated by membrane-anchored metalloproteases. Most of the members of the ADAM (A disintegrin and metalloproteinase) family have proteolytic activity and are actively associated with the process of proteolytic 'shedding' of membrane-bound proteins and hence the rapid modulation of key signals in the tumor microenvironment. Increased ADAM17 expression in NSCLC is associated with aggressive progression and poor prognosis. ADAM17 regulates shedding of multiple key oncogenic growth factors, cytokines and adhesion molecules. Thus, ADAM17 drives pleiotropic pathways that are involved in auto- and paracrine signaling and therefore might represent a relevant target for a combined treatment modality in NSCLC.

We are highly interested to gain additional insights on the mechanism and identification of RT-induced ADAM17-mediated shedding substrates. Therefore, we aim to identify substrates of ADAM17 in the primary tumor microenvironment or metastatic niches that could be druggable targeted and help to sensitize the tumors to RT. To achieve this goal, we will apply the BirA-method on ADAM17 that is a relatively new molecular tool to identify protein-protein interactions (= interactome) due to proximity-dependent labeling of proteins by a promiscuous *Escherichia coli* biotin protein ligase. Promising candidates identified by mass spectometry will be tested *in vitro* in cell cultures and *in vivo* in immune competent orthotopic lung tumor models.

SPECIAL TECHNIQUES AND EQUIPMENT

BioID method, Mass spectrometry, Orthotopic lung cancer model, small animal image-guided radiotherapy device, multicolor flow cytometry