FP53. — INTRA-TUMORAL HETEROGENEITY AND RATIONAL SELECTION OF ANTIGENS FOR TARGETED THERAPY OF LIVER METASTASES.

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Targeted therapies of liver metastases are gaining a major stake in current and future treatment options. However, the malignant lesions are heterogeneous in nature offering niches for cancer cells causing treatment resistance and relapse. Therefore, a rational strategy is needed to select targetable antigens that would overcome this intra-tumoral heterogeneity.

After ethical committee approval, 48 fresh liver metastases of colorectal origin were prospectively collected from patients undergoing liver resection. Here we macroscopically divided the lesion in different zones and generated a unique quantitative picture of the proteome heterogeneity in colorectal carcinoma liver metastases. Particular focus was laid on accessible proteins, a protein subclass comprising cell membrane associated and extracellular proteins. Accordingly, the tissues were ex-vivo biotinylated, affinity purified and analysed for each zone separately using nano-UPLC-MSe proteomics technique. In total over 1500 unique proteins were statistically divided into different patterns of expression.

We have generated a quantitative picture of the proteome heterogeneity in colorectal carcinoma liver metastases. The study offers insight into novel targets but also antigens against which the antibodies are already involved in clinical trials or treatment of liver metastases. Extensive clustering and validation experiments highlight novel markers that offer the potential to homogeneously cover the metastatic lesion and become better targets.

Two such antigens, LTBP2 and TGFBI were selected for functional analysis in colorectal carcinoma cells. In vitro and in vivo experiments showed that in particular TGFBI is relevant for migration and proliferation capacity of colorectal cancer cells. The suppression of this protein led to significant inhibition of tumour growth, crystalizing it as bona fide target for the development of anti-metastases therapies.