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Discovery of Novel Accessible Proteins for Therapeutic Targeting of Hepatocellular Carcinoma

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Introduction: Hepatocellular carcinoma (HCC) is world's sixth most common and third most deadly malignancy. The clinical management of HCC is difficult. Apart from liver transplantation in a minority of operable patients, there is currently no effective treatment to eradicate HCC. On-going clinical trials are exploring predominantly small molecules that have not been specifically tailored for HCC. Such therapies have shown only modest success in other types of tumors. We know today that small molecules (such as tyrosine kinase inhibitors) do not have the ability to selectively accumulate in neoplastic lesions. In contrast to this, monoclonal antibodies (mAb) can achieve good tumor to blood ratios. However, in "naked" format mAb rarely have the necessary toxicity to eradicate the tumor. Antibody-drug conjugates (ADC) are potent derivatives of classical antibodies that are able to deliver cytotoxic payloads to the tumor. Unfortunately, today only one ADC is tested for efficacy in HCC (anti-TROP2 antibody conjugated with irinotecan), suggesting that new ADC-compatible targets for HCC are desperately needed.

Aim: The present study is motivated by this unmet need, aiming at a de novo discovery of accessible tumor biomarkers in HCC. Accessible proteins are membrane-bound and extracellular proteins that are reachable by systemically delivered homing antibodies.

Methods: The isolation of accessible proteins was performed using fresh human HCC tissues as well as matched normal livers from 5 individual patients. Fresh biopsies were first soaked in biotinylation reagent (Sulfo NHS-SS biotin), followed by isolation of target proteins using streptavidin affinity columns. The isolated proteins were further identified and quantified owing to an MS-assisted proteomic approach.

Results: The analysis identified over 1500 potentially accessible proteins, of which at least 200 targets were uniquely expressed in HCC. Bioinformatic evaluation focusing exclusively on proteins with known subcellular localization revealed more than 20 novel therapeutic candidates. Validation studies using immunohistochemistry on larger cohort of patients (N=200) confirmed the overexpression of several selected proteins in HCC.

Conclusions: Current efforts are underway to explore the targeting ability of specific monoclonal antibodies directed against these biomarkers in HCC in vivo models.

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The correlation between imaging and resection specimen of colorectal liver metastases.

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