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Short Communication Open Access

Pharmacoproteomic Identifies Kinase Pathways in Hepatocellular Carcinoma That Drive

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Short Communication

Introduction

Hepatocellular carcinoma is the fourth leading cause of cancer-related death in the world and it can be affected by a multitude of factors, including viral hepatitis, alcoholic cirrhosis, and nonalcoholic steatohepatitis. HCC has one of the fewest druggable genetic changes among solid tumours, limiting therapeutic options for advanced HCC The Cancer Genome Atlas R. Five of the seven FDA-approved medicines for advanced HCC, including the small-molecule medications sorafenib, regorafenib and lenvatinib target protein kinases [1]. The antibodies ramucirumab and cabozantinib as well as cabozan demonstrate the relevance of kinase-dependent signalling networks in HCC progression. However, predictive biomarkers that could guide clinical use of these kinase inhibitors (KIs) are lacking, which is likely one of the reasons for the low response rates of 10%–15%.

We measured drug response signatures in human HCC samples using kinobead/LC-MS, which could be used as candidate prognostic markers for customised treatment. Our findings revealed that the cellular EMT state has a broad impact on kinase expression and activation, as well as different signalling networks and drug response characteristics [2]. We discovered a signalling circuit that induces EMT in HCC cells. The EMT was reversed, replication stress signalling was enhanced, and HCC cells were more sensitive to medicines after genetic knockdown or small-molecule inhibition of these proteins.

Description

The EMT State of HCC Cells Has a Wide Range of Effects on Kinase Inhibitor Responses

We looked for similarities in response pathways across all 299 medications examined in order to discover the main pathways that control responses to a wide range of current and pre-clinical KI medicines. We divided drugs into 11 KI clusters with similar pathway signatures, then calculated mean NES values for 34 representative Reactome terms from a larger panel of 275 scored pathways, followed by unsupervised hierarchical clustering [3-5]. Positive NES values for pathways widely overexpressed in rapidly proliferating cells, such as FGFR, IGF1R, cell-cycle, and mitosis-related pathways, were found in KIs in clusters 5–7 and 9–11. To discover signalling pathways driving HCC drug sensitivity and resistance, we developed a kinome-centric pharmacoproteomics strategy that combined kinome activity patterns and drug responses. Our findings suggest that kinase and interactor phosphorylation states are typically stronger predictors of drug response than mRNA or protein expression, and that phosphorylation events spanning the larger signalling network might predict responses to medicines that target other kinases within these pathways. Our unbiased discovery of pathway-based drug response signatures identified kinase drug targets and proposed sensible medication combinations for the treatment of HCC. We conclude that data on the proteome and PTM expression are critical.

Human HCC and Adjacent Normal Liver Specimens

Patients undergoing liver resection at the University of Washington Medical Center provided primary human HCCs with paired non-tumor livers for study (Seattle, WA, USA). Under the Institutional Review Board guidelines #1852, all patients in this study prospectively agreed to donate liver tissue for research. The samples were snap-frozen in liquid nitrogen and stored at -80°C for further processing under the supervision of Pathology experts. The following characteristics were found in patent samples:

NUAK1 Expression in the Ectopic State

Genecopoeia provided the expression construct expressing full length NUAK1 (NM_ 014840.2) in a lentiviral plasmid.Using Lipofectamine 2000 (Invitrogen, Carlsbad, CA), cell lines were transfected with the NUAK1 plasmid construct and chosen 48 hours later in 4 g/ml puromycin (Invitrogen). Stable cell lines were maintained in DMEM supplemented with 2 g/ml puromycin (see Cell Lines and Tissue Culture Conditions).

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Conflict of Interest

The authors declare that they are no conflict of interest

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