ABSTRACT

INVESTIGATING THE ROLE OF ELEVATED FREE FATTY ACIDS IN EPITHELIAL-MESENCHYMAL

TRANSITION OF HEPATOCELLULAR CARCINOMA

By

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Hepatocellular carcinoma (HCC) is one of the deadliest forms of cancer world-wide w ith steadily increasing incidence and m ortality rates in the United States. Advanced HCC are characterized by increased prevalence of intrahepatic and extrahepatic metastases, and are associated w ith very poor survival rates. Epidemiological studies indicate elevated free fatty acid (FFA) levels, the physiological manifestation of obesity, may be associated w ith higher m ortality rates in HCC patients. Here, we investigated the effects of elevated FFA uptake on the induction of epithelial to mesenchymal transition (EMT) program - a pathway involved in metastatic progression of human cancers. Our initial studies w ith saturated FFA palmitate (PA) revealed a significant loss of the obligate desmosomal protein desmoplakin (DSP) in HepG2 cells, indicating a loss of cell adhesion. We next observed enhanced m igration and invasiveness in HepG2 and Hep3B cells in response to PA treatm ent and confirmed loss of cell adhesion in the tw o cell lines. PA treatm ent resulted in cytotoxicity and expression of EMTmarkers in distinct populations w ithin the treated cells. Additionally, we identified that the W nt/p-catenin and TGF-P signaling pathways were activated, suggesting a possible mechanism of EMT induction by PA. We further assessed the association between CD36, a FFA uptake gene normally expressed at low levels in hepatocytes but found to be elevated in fatty liver, and the activation of EMT program in human HCC. Our analysis revealed a significant association between CD36 and expression of EMT markers in the cancer genome anatomy (TCGA) liver cancer mRNA expression dataset, which was confirmed w ith protein samples from human HCC tum or biopsies. Interestingly, both studies suggested that expression of EMT markers were not correlated w ith body mass index of the patients. Given the role of exogenous FFA uptake in prom oting EMT and metastasis in HCC, we further analyzed somatic mutations, copy number variations, and gene expression profiles of fatty acid uptake and

metabolism genes in context of metastatic progression in >8,000 samples from the TCGA database across 12-different cancer types. Our analysis revealed a significant and previously undocumented role of fatty acid uptake and fatty acid metabolism genes in the metastatic progression of m ultiple human cancers, and demonstrated the utility of genes involved in these pathways as strong prognostic biomarkers w ith significant influence on survival rates.