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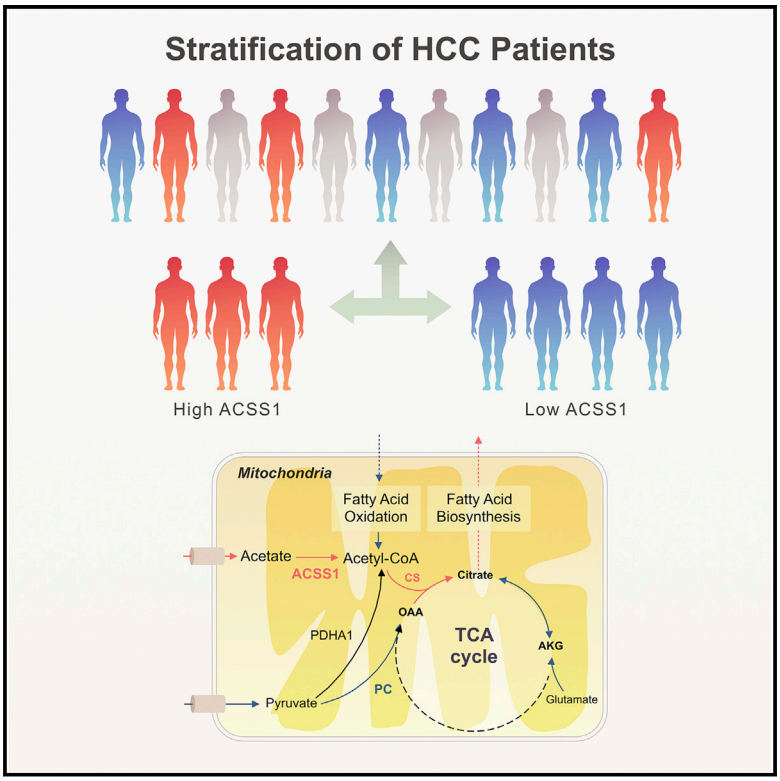
Stratification of Hepatocellular Carcinoma Patients Based on Acetate Utilization

Graphical Abstract



Highlights

- Reconstruction of a genome-scale metabolic model for HCC tumors
- Revealing metabolic alterations in HCC
- Analysis of the heterogeneous expression of ACSS1 and ACSS2 between HCC tumors
- Induction of ACSS1 in murine and human HCC samples under hypoxic conditions

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In Brief

Stratification of HCC patients is vital for the development of effective treatment strategies. Björnson et al. stratify HCC patients based on acetate utilization and find that mitochondrial acetate is a metabolic fuel under hypoxic conditions. This is mediated by ACSS1, which may be a potential therapeutic target for treatment of HCC.

Björnson et al., 2015, Cell Reports *13*, 2014–2026
December 1, 2015
http://dx.doi.org/10.1016/j.celrep.2015.10.045

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Stratification of Hepatocellular Carcinoma Patients Based on Acetate Utilization

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http://dx.doi.org/10.1016/j.celrep.2015.10.045

SUMMARY

Hepatocellular carcinoma (HCC) is a deadly form of liver cancer that is increasingly prevalent. We analyzed global gene expression profiling of 361 HCC tumors and 49 adjacent noncancerous liver samples by means of combinatorial network-based analysis. We investigated the correlation between transcriptome and proteome of HCC and reconstructed a functional genome-scale metabolic model (GEM) for HCC. We identified fundamental metabolic processes required for cell proliferation using the network centric view provided by the GEM. Our analysis revealed tight regulation of fatty acid biosynthesis (FAB) and highly significant deregulation of fatty acid oxidation in HCC. We predicted mitochondrial acetate as an emerging substrate for FAB through upregulation of mitochondrial acetyl-CoA synthetase (ACSS1) in HCC. We analyzed heterogeneous expression of ACSS1 and ACSS2 between HCC patients stratified by high and low ACSS1 and ACSS2 expression and revealed that ACSS1 is associated with tumor growth and malignancy under hypoxic conditions in human HCC.

INTRODUCTION

Hepatocellular carcinoma (HCC) is a deadly form of liver cancer, and it is currently the second leading cause of cancer-related deaths worldwide (European Association For The Study Of The Liver; European Organisation For Research And Treatment Of Cancer, 2012). Despite a number of available treatment strategies, the survival rate for HCC patients is low (Llovet et al., 2008). Considering its rising prevalence, more targeted and effective treatment strategies are highly desirable for HCC.

Cancer development involves major metabolic alterations (Carracedo et al., 2013), and the complexity of metabolism has been captured by the reconstruction of genome-scale metabolic models (GEMs) (Lewis and Abdel-Haleem, 2013; Mardinoglu and Nielsen, 2015; O'Brien et al., 2015; Yizhak et al., 2015), one of the denominators in systems biology, to identify selective anti-cancer drug targets (Agren et al., 2014; Folger et al., 2011). A GEM is the collection of all known biochemical reactions occurring in a given healthy cell or cancer, and each of these reactions is associated with gene products catalyzing these reactions (Mardinoglu et al., 2013a, 2015; Mardinoglu and Nielsen, 2012; Oberhardt et al., 2013; Shoaie and Nielsen, 2014). To unveil the molecular mechanisms underlying cancer, cancer-specific GEMs have been reconstructed (Agren et al., 2012; Gatto et al., 2014; Ghaffari et al., 2015; Mardinoglu et al., 2013b; Yizhak et al., 2014).

Availability of GEMs together with the high-throughput data and methods of data analysis may enable increased understanding of the altered metabolism in cancer. In addition, differential expression (DE) and differential rank conservation (DIRAC) analysis (Eddy et al., 2010) extract different types of information from gene expression data and may complement each other. Here, we identified metabolic differences between 361 HCC tumors and 49 adjacent noncancerous liver tissue samples using global gene expression profiling (RNA sequencing [RNA-seq] data). We reconstructed a population-based functional GEM for HCC tumors by integrating the transcriptome and proteome of HCC and examined the changes in the gene expression data using DE and DIRAC analysis based on the network topology provided by the GEM. We performed DIRAC analysis to identify and measure network-level perturbations based on the relative levels of expression for participating genes (Figure S1; Supplemental Experimental Procedures). Finally, we discovered