Large-Scale Molecular Changes from Dysplastic Nodule to Hepatocellular Carcinoma: Molecular Dissecting and Functional Evaluation of Early Hepatocarcinogenesis

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Hepatocelluar carcinoma (HCC) progression is a stepwise process from pre-neoplastic lesions including low- (LGDN) and high-grade dysplastic nodules (HGDN) to advanced HCC. However, the molecular changes associated with this progression are unclear, and the morphologic cues thought to distinguish the pre-neoplastic lesion from well differentiated HCC are not universally agreed upon. In order to understand the multistep process of hepatocarcinogenesis at the molecular level, we have used oligonucleotide microarrays to investigate the transcription profiles of 50 hepatocellular nodular lesions ranging from LGDN to primary HCCs (Edmondson grade I-Ⅲ). We suggest that gene expression profiles can discriminate not only between dysplastic nodules and overt carcinoma, but also between different histological grades of HCC. From this, we identified 3,084 grade-associated genes, correlated with tumor progression, by combination of one-way ANOVA and one-versus-all test. Using both Diagonal Linear Discriminant Analysis and Support Vector Machines, we identified 240 genes that could accurately classify tumors according to histological grade especially for discriminating LGDN, HGDN and G1 HCC which have difficult problems in morphological diagnosis. We also dissected molecular signature functionally involved in cell-cycle, and proved the causality of molecular changes of these molecules to cancer progression. Our results show that a clear molecular demarcation between dysplastic nodules and overt HCC exists, and that progression from G1 through G3 HCC is associated with changes in gene expression consistent with plausible functional consequences.