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Genomic Analysis of Hepatocarcinogenesis

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Hepatocellular carcinoma (HCC) is the 2nd most prevalent malignancy in Korea. Although it is known as one of the few cancers with well-defined major risk factors, early diagnosis has been hampered by the lack of accurate and sensitive tools. Also, standard clinicopathological classification of HCC has limits in predicting the treatment outcome. Molecular markers that can be used to locate early-stage tumors, distinguish tumor types or stage of tumor development, predict treatment outcome, or monitor the treatment progress should provide powerful tools to overcome current technical barriers in HCC diagnosis and treatment. These markers also provide molecular targets to which therapeutic intervention should be directed. We analyzed the gene expression profiles of 32 paired HCC samples using cDNA microarray chips enriched in liver- and/or stomach-expressed cDNA elements (a total of 47,357 clones). We identified groups of genes that can tell tumors from non-tumors or non-tumors from normal liver, or classify tumors according to clinical parameters such as Edmonson's grade, age, and inflammation grade. These genes were further analyzed using various data mining tools, attempting to describe HCC as molecularly dissectable genomic phenomena. These results will help better understand HCC at genomic scale, and provide a basis for developing efficient diagnostic and therapeutic tools.

S1-04

Complex Regulatory Network of Multiple Protein Factors In Human Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) is a typical hypervascular tumor. Generally, HCC is developed through liver cirrhosis induced by chronic liver injury. This chronic injury leads to changes in the cellular property of the liver and subsequently causes fibrogenesis to demolish normal liver blood system. The catastrophe of the normal liver blood system leads to the shortage of blood circulation in the liver and causes hypoxia. Hypoxia can stimulate angiogenesis to support tumor growth by induction of angiogenic factors. Recently, it has been reported that several hypoxia-regulatory factors are closely involved in angiogenesis of hepatocellular carcinoma. Among them, hypoxia-inducible factor-1 α (HIF-1 α) functions as a master regulator of oxygen and undergoes conformational changes in response to oxygen concentrations. HIF-1 α interacts with several protein factors including PHD, pVHL, ARD-1, and p300/CBP. Under normoxia, the HIF-1 α is rapidly degraded via pVHL-mediated ubiquitin-proteasome pathway. Moreover, hepatitis B virus X protein (HBx) increases the transcriptional activity and protein level of HIF-1 α under both normoxic and hypoxic conditions, and also stimulates angiogenesis. In addition, HBx decreases the binding of pVHL to HIF-1 α and prevents ubiquitin-dependent degradation of HIF-1 α. To identify more protein factors in hepatocellular carcinoma, we constructed a database of HCC related proteins. Protein lists have been extracted from articles of reporting the differentially expressed proteins under the different HCC stages or HCV/HBV infection status. These proteins are classified depending on their expression stages (normal, chronic hepatitis, fibrosis, cirrhosis, dysplastic anver blood system. The catastrophe of the normal liver blood system leads to the shortage of blood circulation in the liver and causes hypoxia. Hypoxia can stimulate angiogenesis to support tumor growth by induction of angiogenic factors. Recently, it has been reported that several hypoxia-regulatory factors are closely involved in angiogenesis of hepatocellular carcinoma. Among them, hypoxia- inducible factor-1 α (HIF-1 α) functions as a master regulator of oxygen and undergoes conformational changes in response to oxygen concentrations. HIF-1 α interacts with several protein factors including PHD, pVHL, ARD-1, and p300/CBP. Under normoxia, the HIF-1 α is rapidly degraded via pVHL-mediated ubiquitin-proteasome pathway. Moreover, hepatitis B virus X protein (HBx) increases the transcriptional activity and protein level of HIF-1 α under both normoxic and hypoxic conditions, and also stimulates angiogenesis. In addition, HBx decreases the binding of pVHL to HIF-1 α and prevents ubiquitin-dependent degradation of HIF-1 α. To identify more protein factors in hepatocellular carcinoma, we constructed a database of HCC related proteins. Protein lists have been extracted from articles of reporting the differentially expressed proteins under the different HCC stages or HCV/HBV infection status. These proteins are classified depending on their expression stages (normal, chronic hepatitis, fibrosis, cirrhosis, dysplastic and HCC I, II, III stages). Using the HCC stage database and AngioDB(Angiogenesis Database), we developed the protein interaction networks of angiogenesis-related proteins involved in HCC development. Collectively, we constructed a complex regulatory network of multiple protein factors which are involved in HCC angiogenesis. Using the regulatory network, we can further study functions of the angiogenesis-related proteins during hepatocarcinogenesis. Therefore, we suggest that the analysis of protein interaction network of HCC can provide new insights into the elucidation of hepatocarcinogenesis and the identification of potential therapeutic target proteins of HCC.