C-3-01

Identification of genes and pathways involved in DNA methylation in hepatocellular carcinoma

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Keywords: DNA methylation, Hepatocellular carcinoma, DNA microarray

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide. Despite major efforts to improve diagnosis and treatment of HCC, therapeutic options remain limited[1]. A role for DNA methylation in the regulation of gene expression was hypothesized many years ago. Recent genetic studies suggest that tumor suppressor genes (TSGs) are often silenced during carcinogenesis through epigenetic modification caused by metylation of promoter CpG island[2]. Therefore, detailed investigation of genes inactivated by DNA methylation in HCC is necessary for the development of novel treatment options for HCC.

In this study, we aimed to identify candidate genes commonly methylated in HCC. We treated eight HCC cell lines by the DNA demethylating agent 5-aza-2'-deoxycytidine (DAC). Comprehensive gene expression analysis revealed that 489 probe sets had more than two-fold up-regulated in at least six DAC-treated cell lines compared to the control cell lines. Moreover, Gene set enrichment analysis (GSEA) of DAC-treated cells suggested that down-regulation of immune response pathways were possibly induced by DNA methylation. Interestingly, chemokine (C-X-C motif) ligand 2 (CXCL2) was included in the 44 probe sets and is associated with immune response. Because immune surveillance is an important host system to inhibit carcinogenesis and thereby down-regulation of CXCL2 might cause immune escape of cancer cells, CXCL2 can be one of the key molecules for cancer progression by DNA methylation.

Our results suggest that these genes and pathways may play an important role in carcinogenesis and disease progress of HCC through inactivation by DNA methylation. Notably, the candidate gene CXCL2 might be an important molecule for further investigation of immune escape in HCC. In our validation studies, we showed that the expression of CXCL2 was down-regulated in HCC tissue as compared to non-tumor tissues. In addition, CXCL2 expression was significantly up-regulated by DAC treatment in HCC cell lines. This suggests that CXCL2 might be an important molecule for further investigation of aberrant methylation in HCC.

References

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