

Inhibition of hepatocellular carcinoma growth by ZBP-89, an epigenetic mechanism

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Increasing evidence indicates that the transcription factor ZBP-89 can inhibit the growth of a number of human tumors including hepatocellular carcinoma (HCC) and colorectal cancer by promoting apoptosis of tumor cells. However, the molecular mechanism responsible is not clear. DNA methyltransferase 1 (DNMT1) and histone deacetylases 3 (HDAC3) are key enzymes in the control of DNA methylation that participates in the regulation of a number of genes related to tumorigenesis and tumor growth. The aim of this study was to explore whether anti-HCC effect of ZBP-89 was related to epigenetic mechanisms. In this study, we used methylation-special PCR to examine the effect of ZBP-89 on DNMT1 and HDAC3, and subsequently on CpG island in gene promoters of HCC cells. Cell function was assessed by measuring cell viability (MTT assay) and apoptosis (TUNEL). The result showed that ZBP-89 significantly inhibited the activities of DNMT1 and HDAC3, resulting in maintenance of histone H3 and H4 acetylation. Using the pro-apoptotic gene Bak as an example, we found that ZBP-89 increased the demethylation of CpG island in the Bak promoter so that the expression of Bak was much enhanced. The increased Bak expression subsequently led to the reduction of tumor cell viability and the increase of apoptotic cell death. In conclusion, ZBP-89 exerts the anti-tumor effect via inhibiting DNMT1 and HDAC3 to enhance the expression of pro-apoptotic molecules such as Bak in HCC cells. (This study was supported by the Research Grants Council of the Hong Kong Special Administrative Regions: CUHK462009. Caiguo Ye, Chris ZY Zhang, Rocky Ho and Paul BS Lai participated in this study).

Biography

George G Chen is a professor in the Department of Surgery, Director of Surgical Research Laboratories, the Chinese University of Hong Kong, Hong Kong. He is also served as a principle investigator at the Hong Kong Cancer Institute. He has extensive experience in cancer research, particularly in the area of apoptosis in hepatocellular carcinoma, lung cancer and thyroid cancer. He has authored or co-authored ~130 papers. He is currently a member of editorial boards or a guest editor of a number of scientific journals and a regular peer-reviewer for several grant agents.

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