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Hypoxia-inducible factor-2a facilitates the expression of ZBP-89 and programmed cell death 4 in hepatocellular carcinoma

The role of hypoxia-inducible factor-2 alpha (HIF-2a) in cancer is debatable, and its status in hepatocellular carcinoma (HCC) is poorly understood. ZBP-89 and programmed cell death 4 (PDCD4) are known to function as suppressors in HCC via stimulating apoptotic-related molecules but inhibiting some key molecules associated with hepatic cancer stem cells. The connection between HIF-2a and ZBP-89/PDCD4 remains elusive. In this study, we assessed the expression of HIF-2a in HCC samples and explored how HIF-2a impacted the levels of ZBP-89 and PDCD in HCC cells. Our results showed that the level of HIF-2a protein in HCC tumor tissues was significantly lower than in non-tumoral tissues. The high expression of HIF-2a in HCC cells was associated with a slower growth rate, whereas cells transfected with HIF-2a shRNA grew faster than the control. The HIF-2a-mediated reduction of the HCC growth was associated with the elevation of pro-apoptotic molecules ZBP-89 and PDCD4. By analysing ZBP-89 and PDCD4 genes, it was found that both ZBP-89 and PDCD4 promoters contained several potential HIF-2a binding sites. The luciferase assay showed that the promoter activities of ZBP-89 and PDCD4 could be significantly increased by HIF-2a overexpression whereas their activities were obviously decreased by blocking HIF-2a. Our data have also shown that ZBP-89 could negatively regulate hepatic cancer stem cells. PDCD4 is also known to restrain the self-renewal of stem cells. In conclusion, our data have demonstrated that the HCC is associated with downregulation of HIF-2a, leading to decreasing the levels of ZBP-89 and PDCD4. The findings suggest that HIF-2a downregulation may facilitate the growth of HCC by reducing ZBP-89 and PDCD4 levels, subsequently inhibiting apoptosis in HCC cells but stimulating hepatic cancer stem cells. (This study was supported by grants from CUHK direct grant (4054308), the Research Grants Council of the Hong Kong Special Administrative Region (14109516) and the National Natural Science Foundation of China (81472339).

Biography

George G Chen is a professor in the Department of Surgery, Director of Surgical Research Laboratories, Faculty of Medicine, the Chinese University of Hong Kong, China. He has extensive experience in cancer research, particularly in the area of liver, lung and thyroid cancers. He has authored or co-authored around 200 papers and has written a number of books or book chapters.

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