Internal Radiotherapy of Liver Cancer with Rat Hepatocarcinoma-Intestine-Pancreas Gene as a Liver Tumor-Specific Promoter

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Résumé en anglais	The hepatocarcinoma-intestine-pancreas (HIP) gene, also called pancreatitis-associated protein-1 (PAP1) or Reg IIIα, is activated in most human hepatocellular carcinomas (HCCs) but not in normal liver, which suggests that HIP regulatory sequence could be used as efficient liver tumor-specific promoters to express a therapeutic polynucleotide in liver cancer. The sodium iodide symporter (NIS), which has recognized therapeutic and reporter gene properties, is appropriate to evaluate the transcriptional strength and specificity of the HIP promoter in HCC. For this purpose, we constructed a recombinant rat HIP–NIS adenoviral vector (AdrHIP-NIS), and evaluated its performance as a mediator of selective radioiodide uptake in tumor hepatocytes. Western blot, immunofluorescence, and iodide uptake assays were performed in AdrHIP-NIS-infected primary hepatocytes and transformed hepatic and nonhepatic cells. Nuclear imaging, tissue counting and immunohistochemistry were performed in normal and HCC-bearing Wistar rats infected with AdrHIP-NIS intratumorally or via the hepatic artery. In AdrHIP-NIS-infected transformed hepatic cells, functional NIS was strongly expressed, as in cells infected with a cytomegalovirus-NIS vector. No NIS expression was found in AdrHIP-NIS-infected normal hepatocytes or transformed nonhepatic cells. In rats bearing multinodular HCC, AdrHIP-NIS triggered functional NIS expression that was preferential in tumor hepatocytes. Administration of 18 mCi of 131I resulted in the destruction of AdrHIP-NIS-injected nodules. This study has identified the rHIP regulatory sequence as a potent liver tumor-specific promoter for the transfer of therapeutic genes, and AdrHIP-NIS-mediated 131I therapy as a valuable option for the treatment of multinodular HCC.
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