UNDERSTANDING THE MECHANISMS OF IGF2 GENE REGULATION IN HEPATOCELLULAR CARCINOMA CELLS

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Hepatocellular carcinoma (HCC) is a leading cause of cancer-related deaths worldwide. HCC has a very well studied etiology, and is associated with chronic hepatic viral infections (hepatitis viruses B and C), alcohol abuse, or other causes of chronic liver damage. Currently, tumor resection and liver transplantation are the only potentially curative treatments available for HCC. However, the presence of extra-hepatic invasion and metastasis makes patients ineligible for these treatments. High IGF2 levels are associated with metastatic HCC, and we recently showed that IGF2-induced signaling through Igf1R stimulates the invasiveness and metastatic phenotype of HCC cells. However, the precise mechanisms by which IGF2 expression is enhanced in HCC are not well understood. IGF2 is an imprinted gene normally expressed from the paternal allele. Loss of imprinting, which activates the normally silent maternal allele, has been implicated as an epigenetic marker for the enhanced risk of human cancer. However, many HCCs that display elevated IGF2 expression levels retain a normal imprinting pattern. Therefore, additional gene regulation mechanisms must also influence IGF2 expression in HCC.

Hypothesis: Long-range genomic interactions are important for the regulation of IGF2 gene expression, and alterations in these long-range interactions lead to elevated IGF2 gene expression in HCC. To address this hypothesis I have utilized chromosome conformation capture carbon copy (5C) technology to elucidate long-range interactions involving the IGF2 promoters in a normal hepatocyte cell line, THLE-2, and an HCC cell line HepG2.