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Epigenetic upregulation of HGF and c-Met in circulating tumor cells drives metastasis in hepatocellular carcinoma

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Abstract

Hepatocyte growth factor (HGF) and its receptor, c-Met, are important regulators of growth and differentiation of healthy hepatocytes. However, upregulation of HGF and c-Met have been associated with tumor progression and metastasis in hepatocellular carcinoma (HCC). Hematogenous dissemination is the most common route for cancer metastasis, but the role of HGF and c-Met in circulating tumor cells (CTCs) is unknown. We have isolated and established a circulating tumor cell line from the peripheral blood of a mouse HCC model. Our studies show that these CTCs have increased expression of HGF and c-Met in comparison to the primary tumor cells. The CTCs display phenotypic evidence of epithelial-mesenchymal transition (EMT) and the EMT appears to be inducible by HGF. Epigenetic analysis of the c-Met promoter identified significant loss of DNA methylation in CTCs which correlated with overexpression of c-Met and increased expression of HGF. Six specific CpG sites of c-Met promoter demethylation were identified. CTCs show significantly increased tumorigenicity and metastatic potential in a novel orthotopic syngeneic model of metastatic HCC. We conclude that during hematogenous dissemination in HCC, CTCs undergo EMT under the influence of increased HGF. This process also involves up regulation of c-Met via promoter demethylation at 6 CpG sites. Consequently, targeting HGF and c-Met expression by CTCs may be a novel non-invasive approach with potential clinical applications in HCC management.

Biography

Olorunseun Ogunwobi, MD, PhD is currently a postdoctoral fellow in Cancer Biology in the Department of Pathology, Immunology and Laboratory Medicine of the University of Florida. His research is currently supported by a NIH T32 fellowship, the American Association for Cancer Research AACR-FNAB Fellows Grant and by the Experimental Pathology Innovative Grant from his department at the University of Florida. He is an author of 23 peer-reviewed research articles in the area of cancer biology. Since 2009, he has been studying the mechanisms of metastasis in solid cancers. His work on hepatocellular carcinoma (HCC) has resulted in six recent publications. His recent article published in Clinical and Experimental Metastasis reported that hepatocyte growth factor promotes development of HCC via induction of epithelial-mesenchymal transition (EMT), a process that has been associated with cancer metastasis. Another recent paper in Journal of Gastroenterology and Hepatology showed that a number of other growth factors are also able to induce EMT in HCC progression. The paper also showed that COX-2 and Akt are involved in EMT induction and progression in HCC. His most recent article entitled “Epigenetic upregulation of HGF and c-Met drives metastasis in hepatocellular carcinoma” was just accepted for publication by PLOS ONE. He has had many opportunities to present his research findings in national and international conferences in the United Kingdom, Denmark, Germany, Spain and in the USA. He is currently on the editorial board of Journal of Cancer Research Updates and has been invited as a guest editor for a special issue of Journal of Liver entitled “Hepatocellular Carcinoma”. He is also an adhoc reviewer for journals such as Carcinogenesis, BMC Cancer, Gut, American Journal of Gastroenterology, Alimentary Pharmacology and Therapeutics, and Journal of Pharmacology and Experimental Therapeutics.