

Overexpression of Hepatoma-Derived Growth Factor (HDGF) is Associated with Invadopodia Formation and Worse Prognosis in Upper Tract Urothelial Carcinoma

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Purpose: Hepatoma-derived growth factor (HDGF) is a nucleus targeted growth factor, it has been reported to exert mitogenic effects on several types of cells and elevated in various types of cancers suggesting an important role in the development and progression of cancers. Our study was designed to elucidate the correlation of HDGF expression and prognosis in patients with upper urinary tract urothelial carcinoma (UTUC). Invadopodia (actin-rich protrusions structures associated with extracellular matrix (ECM) degradation formed by aggressive cancer cells) have an essential role in invasion. Although the role of HDGF in invadopodia has been assumed to signaling and actin assembly, it is incompletely understood. The related molecular mechanisms of HDGF involved in UC invasion and invadopodia formation were investigated. **Patients and Methods:** One hundred and fifty-eight UTUC specimens were analyzed for HDGF by immunohistochemistry. HDGF expression in urothelial cancer cell lines was analyzed by RT-PCR and western blotting. *In vitro* characterizations of the cellular function of recombinant HDGF in epithelial-mesenchymal transition (EMT) and tumorigenic behaviors by trans-well assay and colony formation assay, respectively. The role of HDGF signaling on regulates invadopodia formation and ECM degradation was assessed by gelatin matrix degradation assay. **Results and Conclusions:** Overexpression of HDGF was present in 74 patients (46.8%). A positive HDGF expression was significantly associated with higher disease progression ($p = 0.036$) and cancer-related death rates ($p = 0.001$). *In vitro* study showed that overexpression of HDGF in UC cells could significantly increase their cellular proliferation, colonies formation, migration, invasion and invadopodia formation through the PI3K/AKT pathway. Knockdown of HDGF high expression UC cells with its specific shRNA inhibited the growth ability using colonies formation experiments. Our study demonstrates that HDGF overexpression is associated with aggressive biological behavior of UC cells, act via the PI3K/AKT pathway. HDGF expression status may represent a prognostic prediction biomarker for patients with invasive UTUC after nephroureterectomy. Further investigating the potential therapeutic role of HDGF in the treatment of UC patients is undertaken.