Hepatoma derived growth factor

Hepatoma-derived growth factor (HDGF) also known as high mobility group protein 1-like 2 (HMG-1L2) is a protein that in humans is encoded by the HDGF gene.

Hepatoma-derived growth factor (HDGF), a potential predictive and prognostic marker in several human cancers, is the firstly reported member of the HDGF family of proteins containing a well-conserved N-terminal amino acid sequence. HDGF is implicated in tumorigenesis by direct angiogenic activity, and its expression is correlated with aggressive biological ability of cancer cells including proliferation and angiogenesis.

Gliomas

HDGF is overexpressed in gliomas as compared to normal brain.

HDGF knockdown significantly inhibited the malignant phenotype of U87 cells, including the colony formation, migration and invasion in vitro, as well as tumorigenesis in vivo. The data also suggest that hepatocyte growth factor/scatter factor (HGF/SF) may contribute to the HDGF-associated aggressive behavior of glioma cells [1)].

Findings of novel glioblastoma stem cell (GSC) -secreted molecules with pro-angiogenic properties (Semaphorin 3A, hepatoma derived growth factor) open the path to the design of a concerted attack of glioblastoma vasculature that could overcome the development of resistance to single-targeted therapies while keeping away the toxicity of the treatments [2)].

GSC-conditioned medium induced neoangiogenesis, whereas HDGF-targeting siRNAs abrogated this effect. Altogether, the results identify a novel candidate, by which GSCs can support neoangiogenesis, a high-grade glioma hallmark. comparative proteomic analysis is useful to decipher molecular pathways, which underlie GSC properties [3)]

HDGF is a mitogenic growth factor in glioma progression and can be a useful prognostic marker for GBM and therapeutic target for clinical management of glioma in the future [4)].

Song et al. analyzed the molecular mechanisms of HDGF action in gliomas. HDGF was downregulated in normal brain tissue as compared to glioma specimens at both the mRNA and the protein levels. In glioma samples, increased HDGF expression was associated with disease progression. Knocking down HDGF expression not only significantly decreased cellular proliferation, migration, invasion, and tumorigenesis, but also markedly enhanced temozolomide (TMZ)-induced cytotoxicity and apoptosis in glioma cells. Mechanistic analyses revealed that CCND1, c-myc, and TGF-β were downregulated after stable HDGF knockdown in the U251 and U87 glioma cells. HDGF knockdown restored E-cadherin expression and suppressed mesenchymal cell markers such as vimentin, β-catenin, and N-cadherin. The expression of cleaved caspase-3 increased, while Bcl2 decreased in each cell line following treatment with shHDGF and TMZ, as compared to TMZ alone. Furthermore, RNAi-based knockdown study revealed that HDGF is probably involved in the activation of both the PI3K/Akt and the TGF-β signaling pathways. Together, the data suggested that HDGF regulates glioma cell growth, apoptosis and Epithelial-mesenchymal-transition (EMT) probably through the Akt and the TGF-β signaling pathways. These results provide evidence that targeting HDGF or its downstream targets may lead to novel therapies for gliomas [5)].

Studies suggest that while blood vessels support glioma stem cells, these tumor cells in turn may regulate and contribute to the tumor vasculature by transdifferentiating into endothelial cells directly or through the secretion of regulatory growth factors such as vascular endothelial growth factor (VEGF) and hepatoma derived growth factor (HDGF) [6].

Spinal cord

Hepatoma-derived growth factor-2 (HDGF-2) is expressed in neurons, astrocytes and oligodendrocytes of the adult mouse brain. However, it has remained elusive whether HDGF-2 is expressed in the spinal cord and is involved in the its development and repair. In a study, the expression of HDGF-2 was investigated in rat spinal cords at different developmental stages and following spinal cord injury (SCI). Protein levels of HDGF-2 were examined using western blot analysis, while the distribution pattern and cell populations of HDGF-2 protein expression were characterized using immunohistochemistry. Western blot analysis demonstrated that the levels of HDGF-2 protein expression were the greatest in the spinal cord on embryonic day 19, and were also highly expressed in rat spinal cords on post-natal day 7 (P7); however, they were low at P14 and not detectable at two months. HDGF-2 expression was significantly upregulated in the embryonic spinal cord and injured spinal cord. By contrast, the expression of HDGF-2 was low in uninjured adult spinal cords. HDGF-2 expression in the fetal rat spinal cord and injured spinal cord was significantly higher than that in uninjured adult spinal cord tissues ($P<0.05$). The number of cells positive for HDGF-2 was 141±62, 107±33 and 92±18 at days 1, 21 and 45 following SCI, respectively, as opposed to 50±9 in uninjured rats, and a significant difference was identified between the different time-points following SCI ($P<0.01$). In conclusion, the overexpression of HDGF-2 in the embryonic spinal cord and injured spinal cord may be involved in fetal spinal cord development and repair of SCI, respectively [7].

Lymphoma

HDGF may be a valuable factor in progression and prognosis for primary central nervous system lymphoma (PCNSL) through its angiogenic and proliferative activity. So, HDGF, CD31 and Ki67 expression in the specimens of 60 patients suffering from PCNSL was investigated by immunohistochemistry in this study. Their correlations with clinicopathologic features and prognosis were evaluated to determine whether HDGF, CD31 and Ki67 expression levels correlate with the prognosis of the 60 patients suffering from PCNSL. We found that all PCNSL specimens showed HDGF, CD31 and Ki67 expression with different expression levels. Statistical analysis showed that HDGF had a positive correlation with CD31, but not with Ki67. Patients with higher HDGF and CD31 expression level had poorer overall survival rates than those with lower expression levels of HDGF and CD31, while Ki67 expression level did not correlate with overall survival. Multivariate analysis revealed that postoperative adjuvant chemotherapy and high expression of HDGF was independent prognostic indicator of patient survival [8].

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