JAG1

Jagged1 (JAG1) is one of five cell surface proteins (ligands) that interact with 4 receptors in the mammalian Notch signaling pathway. The Notch Signaling Pathway is a highly conserved pathway that functions to establish and regulate cell fate decisions in many organ systems. Once the JAG1-NOTCH (receptor-ligand) interactions take place, a cascade of proteolytic cleavages is triggered resulting in activation of the transcription for downstream target genes. Located on human chromosome 20, the JAG1 gene is expressed in multiple organ systems in the body and causes the autosomal dominant disorder Alagille syndrome (ALGS) resulting from loss of function mutations within the gene. JAG1 has also been designated as CD339 (cluster of differentiation 339).

Jagged1 has been shown to promote glioma stem cells in glioblastoma.

Survival data from R2 genomics analysis, the Cancer Genome Atlas (TCGA), the Chinese Glioma Genome Atlas (CGGA) and visualization platform database were used to evaluate the effects of Jagged1 on overall patient survival. Hai et al., investigated Jagged1 induced the glioma stem cells invasion by matrix degradation assays and Transwell cell invasion assays in vitro, then they further explored the underlying molecular mechanisms using Co-immunoprecipitation (co-IP) analysis.

High expression of Jagged1 in human glioma was associated with poor survival. Clinical data analysis showed that the Jagged1 was positively correlated with NF-κB(p65). Jagged1-induced invasion of glioma stem cells through activation of NF-κB(p65) pathway. In vivo, knockdown of Jagged1 could suppress the tumorigenicity of GICs cells through NF-κB(p65) signaling.

Insights gained from these findings suggest that Jagged1 plays an important oncogenic role in GICs malignancy by activation of NF-κB(p65) signaling, and Jagged1 could be employed as an effective therapeutic target for GICs [1)].

Ten hemangioblastomas were investigated immunohistochemically. CD44, a mesenchymal stem cell marker, was detected in stromal cells of all cases, suggesting that stromal cells have mesenchymal stem cell-like properties. Neither CD31 nor α-SMA was expressed in stromal cells, suggesting that stromal cells have not acquired differentiated vascular cell properties. Both ephrin-B2 and EphB4, immature vascular cell markers, were detected in stromal cells of all cases. Jagged1, Notch1, and Hesr2/Hey2, which are known to be detected in both immature endothelial cells and mural cells, were expressed in stromal cells of all cases. Notch3, which is known to be detected in differentiating mural cells, was also expressed in all cases. These results suggest that stromal cells also have vascular progenitor cell properties. In conclusion, stromal cells of hemangioblastomas exhibit mesenchymal stem cell-derived vascular progenitor cell properties [2)].

Delta-like ligand 4 (DLL4) and Jagged1 (JAG1), 2 vascular Notch ligands, are involved in the process of tumor angiogenesis. The present study investigates their relationship with microvascularization and the prognostic effect in primary glioblastoma.

Tumor tissues from 61 glioblastomas were analyzed using immunohistochemistry for DLL4/JAG1

expression and microvascular formations. The correlations between DLL4/JAG1 and microvascularization were analyzed. The survival probabilities were computed using the Kaplan-Meier method. The Cox proportional hazards regression model was used for multivariate analysis of time to progression (TTP) and overall survival (OS).

The results showed increased DLL4 and JAG1 expression in glioblastoma tissues. Five types of basic microvascular formations, including microvascular sprouting, vascular cluster, vascular garland, glomeruloid vascular proliferation, and vasculogenic mimicry, were detected. Glioblastomas with the type I microvascular pattern (MVP) that displayed prominent microvascular sprouting and vascular clusters tended to have higher DLL4 expression, whereas those with the type II MVP that had numerous vascular garlands, glomeruloid vascular proliferations, and vasculogenic mimicries showed upregulated JAG1 expression. Univariate analysis documented that high DLL4 expression, high JAG1 expression, and type II (MVP) were statistically associated with reduced TTP and OS. Multivariate analysis confirmed high DLL4 expression, high JAG1 expression, and type II MVP as significant prognostic factors for both shorter TTP and OS, independent of age, Karnofsky performance scale, and other molecular markers (vascular endothelial growth factor, Ki67, and P53).

DLL4 and JAG1 may have opposing effects on tumor angiogenesis in glioblastoma. The Notch pathway may be a new target for antiangiogenic therapy in glioblastoma [3].

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