Two cell lines, J3T-1 and J3T-2, were derived from the same parental canine glioma cell line, J3T. These cells were inoculated to establish brain tumors in athymic mice and rats. Pathologic samples of these animal gliomas were examined to analyze invasive patterns in relation to angiogenesis and were compared with human glioblastoma samples. The molecular profiles of these cell lines were also shown.

Histologically, J3T-1 and J3T-2 tumors exhibited different invasive patterns. J3T-1 cells clustered around newly developed vessels at tumor borders, whereas J3T-2 cells showed diffuse single-cell infiltration into surrounding healthy parenchyma. In human malignant glioma samples, both types of invasion were observed concomitantly. Molecular profiles of these cell lines were analyzed by immunocytochemistry and with a quantitative reverse transcription-polymerase chain reaction. Vascular endothelial growth factor, matrix metalloproteinase-9, hypoxia-inducible factor-1 and platelet-derived growth factor were overexpressed in J3T-1 cells rather than in J3T-2 cells, whereas integrin $\alpha\nu\beta$ 3, matrix metalloproteinase-2, nestin, and secreted protein acidic and rich in cysteine were overexpressed in J3T-1 cells.

These animal models histologically recapitulated two invasive and angiogenic phenotypes, namely angiogenesis-dependent and angiogenesis-independent invasion, also observed in human glioblastoma. These cell lines provided a reproducible in vitro and in vivo system to analyze the mechanisms of invasion and angiogenesis in glioma progression ¹⁾.

Onishi et al. established a pair of animal models (J3T-1 and J3T-2) with different invasive and angiogenic phenotypes and demonstrated that annexin A2 is expressed at higher levels in J3T-1 than J3T-2 cells. The function of annexin A2 in relation to angiogenesis and invasion was investigated using these models. Stable silencing or overexpression of annexin A2 in J3T-1 and J3T-2 cells (J3T-1shA and J3T-2A cells) was established and used. Thirty human glioblastoma samples were evaluated for expression of annexin A2, vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). Immunohistochemical and quantitative reverse-transcription polymerase chain reaction analyses revealed higher expression of annexin A2, VEGF and PDGF in J3T-1 and J3T-2A cells. Cultured J3T-1 and J3T-2A cells exhibited higher adhesive ability to endothelial cells. Histopathological analysis of animal brain tumors revealed that J3T-1 and J3T-2A tumors displayed marked angiogenesis and invasion along the neovasculature, whereas J3T-2 and J3T-1shA tumors exhibited diffuse, infiltrative invasion without angiogenesis. Positive expression of annexin A2 was observed in tumor cells surrounding dilated vessels in 25/30 human glioblastoma specimens. Our results reveal that the phenotype of glioma invasion is closely related to angiogenesis. We identify annexin A2 as a factor regulating angiogenesis and invasion of malignant gliomas².

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