論　文　要　旨

ヒトグリオーマにおける Wnt-5a と MMP-2 の役割の検討

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Wnts are secreted ligands which consist of 19 members in humans, regulate cell proliferation, differentiation, motility, and fate in many stages including embryonic stage and tumorigenesis. Wnts bind to cell surface receptors named Frizzleds and LRPs, and transduce their signals through β-catenin-dependent and -independent intracellular pathways.

Gliomas are one of the most common intracranial tumors. Gliomas exhibit a progression associated with widespread infiltration into surrounding neuronal tissues. However, the molecular mechanisms that stimulate the invasion of glioma cells are not fully understood. We established two cell lines from human glioma cases and analyzed the expression of all Wnt and Frizzled members in these cell lines and other well-known glioma cell lines, by real-time PCR study. The mRNA of Wnt -5a, -7b, Frizzled -2, -6, and -7 were over-expressed in glioma cells. The elevation of Wnt-5a expression was most remarkable. Although Wnt-5a is reported to have oncogenic and antioncogenic activity in several cancers, the role of Wnt-5a signaling in human glioma cells remains unclear.

Immunohistochemical study also revealed high expression of Wnt-5a in 26 (79%) of 33 human glioma cases. The positivity of Wnt-5a expression was correlated with clinical grade.

Knockdown of Wnt-5a expression suppressed migration, invasion, and expression of matrix metalloproteinase-2 of glioma cells. Reciprocally, treatment with purified Wnt-5a ligand resulted in stimulation of cell migration and invasion. MMP-2 inhibitor suppressed the Wnt-5a-dependent invasion of U251 cells. These results suggested that Wnt-5a is not only a prognostic factor but also a therapeutic target molecule in gliomas to prevent tumor cell infiltration.