Angiogenesis is the first regulatory step of tumor progression. Herein, we report on some findings that show that β1,6-N-acetylg glucosaminyltransferase V (GnT-V) functions as an inducer of angiogenesis that has a novel and completely different function from the original function of glycosyltransferase. A secreted type of GnT-V protein itself promoted angiogenesis in vitro and in vivo at physiological concentrations. The highly basic domain of GnT-V induced the release of fibroblast growth factor-2 from heparan sulfate proteoglycan on the cell surface and/or extracellular matrix, leading to angiogenesis. These findings provide some novel information on the relationship between GnT-V and tumor metastasis. The inhibition of GnT-V secretion or its expression represents a novel potential strategy for the inhibition of tumor angiogenesis.

Angiogenesis represents an obligatory step in cancer progression (1, 2). A variety of factors, such as fibroblast growth factor-2 (FGF-2), vascular endothelial growth factor (VEGF) and interleukin-8, contribute to tumor growth. The production of these factors and cytokines is controlled by complicated mechanisms, which include increased gene expression, posttranslational modifications, and interactions with the extracellular matrix.

Many growth factors and their receptors, some of which play a role in tumor angiogenesis, are glycoproteins. Recent studies employing glycosyltransferase gene manipulation have revealed that changes in the oligosaccharide structure of these receptors bring about alterations in intracellular signaling, thus leading to cellular transformation (3–6). β1,6-N-acetylg glucosaminyltransferase V (GnT-V) or mannoside acetylglucosaminyltransferase V (Mgaat5), which catalyzes the formation of N-acetylg glucosaminyltransferase V (GnT-V) functions as an inducer of angiogenesis without mediation of glycosylation.

Clinical studies have shown increases in GnT-V activity in breast and hepatocellular carcinomas (10, 11). In human breast cancer cells, a positive correlation was observed between GnT-V activity and tumor size (11). We have found that the expression of GnT-V in human colon cancer tissues was correlated with a poor prognosis and distant metastasis (12). This suggests that GnT-V level should be indicative of a poor prognosis in cases of colorectal cancer. These results strongly suggest that GnT-V plays a pivotal role in tumor malignancy. However, the detailed mechanisms of the regulation via GnT-V with respect to tumor size or metastasis remain unknown.

To address this issue, we established GnT-V transfectants and examined the metastatic potentials of these cells. In the course of this study, we found that GnT-V transfectants induced dramatic increase in angiogenic activity. The induction of tumor angiogenesis by GnT-V is thought to be due to 1) increases in the expression/production of angiogenic factors, 2) changes in their function via the addition of β1–6 branching, and 3) other unknown mechanisms. In the present study, we have investigated the mechanisms of tumor angiogenesis by GnT-V, and the findings herein show that a secreted type of GnT-V itself was able to induce angiogenesis with no detectable mediation of glycosylation. In addition, we also found that a basic domain in GnT-V caused the direct release of FGF-2 from heparan sulfate proteoglycan (HSPG) on the cell surface and/or extracellular matrix. Our findings here strongly suggest that GnT-V is a bifunctional protein and that a secreted type of GnT-V protein itself plays a critical role in tumor angiogenesis, acting as an angiogenic cofactor of FGF-2.
HUVEC Proliferation Assay—HUVEC were seeded in a 96-well plate coated with type I collagen (2 × 10^3 cells/well). After 24 h, the medium was replaced with MCDB131 medium containing 0.1% bovine serum albumin and starved for 24 h. The medium was then replaced with the conditioned medium from glycosyltransferase transfectants or MCDB131 medium containing human FGF-2 (Dainippon Pharmaceutical Co., Ltd.), GnT-V73, GnT-V188, or GnT-V436, with or without a neutralizing antibody against FGF-2 (R & D systems). After 24 h, the cells were incubated with [3H]thymidine (1 Ci/ml) for 8 h. Incorporation was evaluated by a Micro96 Harvester (SKATRON) and then analyzed with a MicroBeta-Counter (Wallac). The results represent the average ± S.E. of samples assayed in six wells. All experiments were repeated at least three times, and essentially the same results were obtained in each case.

Preparation of Purified Recombinant GnT-V—Two types of GnT-V proteins, GnT-V73 and GnT-V188, both of which are soluble forms, were prepared in a baculovirus-insect cell system (16). For the construction of a transfer plasmid for GnT-V73, the plasmid for GnT-V187 was digested with EcoRI and EagI. The resulting 1521-bp fragment, which includes Glu234–Leu741 of hGnT-V and the C terminus polyhistidine tag, was then ligated into the EcoRI-EagI site of a transfer vector, pAcGP67-A (PharMingen). For the construction of a transfer plasmid for GnT-V436, the plasmid for GnT-V187 was digested with EcoRV and EagI. The resulting 912-bp fragment, which includes Ile437–Leu741 of hGnT-V and the C terminus polyhistidine-tag, was then ligated into the EcoRV-EagI site of the pAcGP67-A vector. The resulting transfer plasmids were transfected into Sf21 cells in order to produce a recombinant enzyme derived from the infected Sf21 cells in a baculovirus-insect cell system (16).

SDS-PAGE was performed according to Laemmli (18). Each GnT-V mutant protein (100 ng) was subjected to 10% SDS-PAGE under reducing conditions. The proteins were visualized by silver staining.

Peptide Synthesis—The KRKRKK peptide, corresponding to amino acids 264–269 of human GnT-V, and the FSGGPL peptide (amino acids 291–296) were synthesized using a Peptide Synthesizer A432 (Applied Biosystems). They were purified using reverse-phase high performance liquid chromatography, and their mass and purity were verified by matrix-assisted laser desorption ionization time-of-flight mass spectrometry (Voyager-DE™ RP; PerSeptive Biosystems).

FGF-2 Measurement—The concentration of FGF-2 was measured as described previously (19). HUVEC cells, seeded at 5 × 10^4 cells/well onto collagen-coated 12-well plates, were washed twice with PBS, and then the medium was then replaced with MCDB131 plus 0.1% BSA (0.5 ml/well), in the presence or absence of each molecule: GnT-V73, GnT-V436, the KRKRKK peptide, the FSGGPL peptide, and heparin. Cells were incubated for 2 h on a rotating plate at 4 °C. The supernatants were collected and centrifuged at 3000 rpm for 5 min at 4 °C to remove debris. These samples were assayed using an FGF-2 enzyme-linked immunosorbent assay system (R & D Systems) according to the manufacturer’s recommendations.

RESULTS

Transplantation of GnT-V Transfectants Induces Hypervascularization in Athymic Mice—Our previous studies demonstrated that the expression level of GnT-V is highly correlated with a poor prognosis in colorectal cancer (12). Therefore, we established stable transfectants of it using the human colon cancer cell line WiDr, along with control transfectants of β1,4-
N-acetylglucosaminyltransferase-III and α1,6-fucosyltransferase. WiDr cells express the above glycosyltransferases at very low or negligible levels. When these transfectants were transplanted to athymic mice, transplanted tumors of GnT-V transfectants showed a dramatic hypervascularization, compared with the other transplants (Fig. 1A).

GnT-V Transfectants Induced Angiogenesis—To verify the induction of angiogenesis by the GnT-V transfectants, the chorioallantoic membrane of chick embryo (CAM assay) was employed (14, 15). An increased invasion of blood capillaries into the collagen sponge was observed only in the case of the GnT-V transfectants (Fig. 1B). This angiogenesis was also observed when the GnT-V gene was transiently expressed in WiDr, COS-1, and Chinese hamster ovary cells (data not shown). These data suggest that the induction of angiogenesis is a common effect of GnT-V gene transfection rather than a unique phenomenon limited to the WiDr clones.

Conditioned Medium from GnT-V Transfectants Stimulates HUVEC Proliferation—To evaluate the induction of angiogenesis in the GnT-V transfectants, we measured their effects on DNA synthesis in human umbilical vein epithelial cells (HUVEC) (20). DNA synthesis of HUVEC was increased as the result of replacement with the conditioned medium from the GnT-V transfectants, whereas no effects were detectable when the conditioned medium from the other transfectants was used (Fig. 1C). These data indicate that the GnT-V transfectants secreted a growth-stimulating factor for HUVEC. The addition of fresh medium (CTR) increased the HUVEC proliferation to a higher level than that of the conditioned medium from the GnT-V transfectants. This is probably due to a supply of growth-stimulating factors such as FGF-2 that are contained in fetal bovine serum.

Effect of Recombinant GnT-V on HUVEC Proliferation—Next, angiogenic activity in the conditioned medium from the GnT-V transfectants was characterized using column chromatography, monitoring HUVEC proliferation-stimulating activity. With heparin affinity chromatography, a high activity fraction was eluted with 0.3 M NaCl (data not shown). This characteristic is completely different from hitherto known angiogenic factors (e.g. FGF-1, FGF-2, VEGF, placental growth factor (PlGF), and hepatocyte growth factor), which are eluted with 0.8–1.5 M NaCl (21–25). When Western blot analysis of the eluted fractions was performed using an anti-GnT-V antibody, its reactivity corresponded to the HUVEC proliferation activity (data not shown). It is known that GnT-V, as well as other glycosyltransferases, is secreted from tumor cells (26–30), although the physiological significance of this remains unknown. To address the hypothesis that a secreted type of GnT-V itself induces the proliferation of HUVEC, we prepared a special type of recombinant GnT-V, referred to as GnT-VΔ73, which lacks the transmembrane domain but in which glycosyltransferase activity is retained (16). HUVEC proliferation was increased as a result of the administration of GnT-VΔ73 in a dose-dependent manner (Fig. 2A). The utilized concentration appears to be within the physiological range. The concentration of GnT-V in conditioned medium from the GnT-V transfectants

![Figure 2](http://www.jbc.org/)

**Figure 2.** Purified recombinant GnT-V proteins accelerate HUVEC proliferation. A, HUVEC proliferation promoted by the administration of GnT-VΔ73. B, constructs of deletion mutants of GnT-V. Black box, the basic region; TM, the transmembrane domain; Stem, stem region of GnT-V. C, SDS-PAGE of purified GnT-V mutants. D, HUVEC proliferation assay after the addition of 100 ng/ml each purified GnT-V mutant protein.
was determined to be 140 ng/ml on the basis of the specific activity of GnT-V/H9004. Furthermore, conditioned medium from B16-F10 mouse melanoma cells, which have a high endogenous GnT-V activity, contained 110 ng/ml GnT-V. B16-F10 cells also showed an angiogenic activity similar to the GnT-V transfec-
tants in the CAM assay (data not shown), suggesting that the GnT-V secreted from B16-F10 cells can stimulate angiogenesis in this assay system. In addition, the administration of recom-
binary 1,6-fucosyltransferase indicated the absence of any HUVEC growth-stimulating activity (data not shown). These data indicate that a secreted type of GnT-V within the physi-
ological concentration range has growth-stimulating activity for HUVEC.

**Domain Analysis of GnT-V Affecting HUVEC Prolifera-
tion**—To determine which domain of GnT-V contains the HUVEC growth-stimulating activity, we analyzed several types of deletion mutants of GnT-V (Fig. 2, B and C). GnT-V/H9004, GnT-V/D183, ∆D183, and ∆D233 mutants stimulated HUVEC proliferation, whereas ∆D436 did not (Fig. 2D). GnT-V/D183 and ∆D183 have GlcNAc transferase activity, but ∆D233 and ∆D436 do not. These data indicate that the HUVEC growth-stimulating activity is located in the region corresponding to amino acids 234–436 of GnT-V, which does not encompass glycosyltransferase activity.

**Identification of a Basic Amino Acid-clustered Region of GnT-V to Induce Angiogenesis**—There is a markedly basic re-
gion, corresponding to amino acids 254–269, of human GnT-V, whose sequence, KSLAEKQNLEKRKRKK, is very similar to the sequence of amino acid 142–157 of VEGF_{169} (21) (Fig. 3A). In addition, the context of basic amino acids in this region is conserved in PIGF-2 and heparin binding type epidermal growth factor-like growth factor (HB-EGF) and serves as a heparin-binding motif (21). Barillari et al. (19) reported that a basic peptide, GRGKRR, derived from the sequence of PIGF-2, induced the growth of endothelial cells by releasing FGF-2 from HSPG on the cell surface and/or extracellular matrix. Therefore, we synthesized a basic peptide, KRKRKK, corresponding to amino acids 264–269 of GnT-V and a nonbasic control pep-
tide, FSGGPL (corresponding to amino acids 291–296 of GnT-V), and examined their effects on the growth of HUVEC. The amount of FGF-2 released from HUVEC after treatment with GnT-V/H9004, GnT-V/∆D36, KRKRKK peptide, and heparin (30 μg/ml) was measured after various truncated GnT-Vs and synthesized peptides were administrated to a culture medium of HUVEC at 4 °C. GnT-V/H9004 and peptide KRKRKK induced the release of FGF-2, whereas GnT-V/∆D436 and peptide FSGGPL had no effect (Fig. 3B). Both GnT-V/∆D188 and ∆D233, as well as GnT-V/∆D183, also induced the release of FGF-2 (data not shown). Similarly, heparin, which is known to release HSPG-
bound molecules by competing for their heparin-binding site (31), also induced the release of FGF-2. The phosphoryl-
ation of FGF receptors on HUVEC by stimulation of the released FGF-2 was confirmed (data not shown). The peptide KRKRKK promoted the growth of HUVEC to an extent sim-
ilar to GnT-V/H9004 (Fig. 3C). This effect was completely sup-
pressed by the co-addition of a neutralizing antibody against FGF-2 (Fig. 3C). These results suggest that the KRKRKK region is sufficient for HUVEC growth-stimulating activity and that the GnT-V protein stimulates angiogenesis by re-
leasing FGF-2 from HSPG on endothelial cells via the action of the basic region of the protein.

**In Vivo Angiogenesis by GnT-V Protein**—The induction of angiogenesis was also observed in other *in vitro* angiogenic assays, such as the capillary-like tube formation (32) and the migration assays (33) using HUVEC (data not shown). In order to investigate the angiogenic activity of GnT-V *ex vivo*, a CAM assay using GnT-VΔ73 protein was performed. GnT-VΔ73 induced angiogenesis of chick microvessels as well as FGF-2 (Fig. 4). Moreover, the KRKRKK peptide even induced a similar angiogenesis, and the induction of angiogenesis by GnT-VΔ73 and peptide KRKRKK was inhibited by treatment with a neutralizing antibody against FGF-2. In contrast, neither GnTVΔ436 nor the control peptide had any angiogenic activity. These results indicate that a secreted type of GnT-V and GnT-V-derived peptide KRKRKK induce angiogenesis via the action of FGF-2. Considering the results relative to HUVEC proliferation, the basic region of GnT-V may cause the release of FGF-2 from HSPG on endothelial cells.

**DISCUSSION**

Angiogenesis is one of the key regulatory steps necessary for tumor malignancy. Several endogenous stimulators and inhibitors of angiogenesis have been identified, and the net balance of these regulators represents the angiogenic phenotype of tumor cells. These include several types of molecules, the functions of which were originally thought to be related to events other than angiogenesis. For instance, angiostatin and endostatin are produced by the proteolysis from plasminogen and type XVIII collagen, respectively (34, 35). In the present study, we found that a secreted type of GnT-V protein induces angiogenesis that is unrelated to the usual glycosyltransferase activity of GnT-V. Although a variety of previous studies indicate that GnT-V is directly linked to tumor metastasis, the mechanistic details of its action at the molecular level remain unknown (6–9). Dennis’s group reported that oligosaccharide structures that are modified by GnT-V on an integrin or T cell receptor affect cell-cell or cell-extracellular matrix interactions in the processes of tumor metastasis and the immune system (7, 36). The present study proposes a new mechanism of GnT-V-related tumor metastasis, which is not mediated by glycosylation. Namely, it appears that GnT-V is capable of acting as a bifunctional protein. GnT-V is a Golgi enzyme but is also secreted by some cultivated cells (26, 27). The concentration of GnT-V sufficient to induce angiogenesis is within the range of concentration that is actually observed in the conditioned medium of B16-F10 cells. Our hypothesis regarding the action of GnT-V in angiogenesis is schematically summarized in Fig. 5. It is thought that GnT-V secreted from cancer cells...
A Secreted Type of GnT-V Induces Angiogenesis

Ets-1 is one of the most important transcriptional factors in up-regulating GnT-V gene expression (41). Ets-1 may be a target for suppressing GnT-V expression. The third is to inhibit the secretion of GnT-V in cancer cells, although the secretion mechanism remains to be solved. The fourth is to mask the basic domain of GnT-V with some reactive acidic reagents. The fifth is the enhancement of the degradation of the secreted GnT-V by proteolysis. First, the issue of whether GnT-V contributes to cancer progression as a glycosyltransferase or an angiogenic factor needs to be determined in individual cancer cases. A specific inhibitor for the N-acetylgalactosaminyltransferase reaction may solve this problem. In conclusion, we report on a novel mechanism in which a secreted type of GnT-V protein itself plays a critical role in tumor angiogenesis, acting as an angiogenic cofactor of FGF-2.

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Fig. 5. Schematic illustration of the induction of tumor angiogenesis by secreted GnT-V. A secreted type of GnT-V that contains the basic amino acid-clustered domain competes with FGF-2 to bind HSPG to the cell surface, resulting in the release of FGF-2 and stimulation of its receptor on the target cells.
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A Secreted Type of β1,6-N-Acetylglucosaminyltransferase V (GnT-V) Induces Tumor Angiogenesis without Mediation of Glycosylation: A NOVEL FUNCTION OF GnT-V DISTINCT FROM THE ORIGINAL GLYCOSYLTRANSFERASE ACTIVITY

Takashi Saito, Eiji Miyoshi, Ken Sasai, Norihiko Nakano, Hironobu Eguchi, Koich Honke and Naoyuki Taniguchi

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