Activation of Cancer Cell Migration and Invasion by Ectopic Synthesis of Coagulation Factor VII

Shiro Koizume,1 Ming-Shou Jin,1 Etsuko Miyagi,2 Fumiki Hirahara,2 Yoshiyasu Nakamura,1 Jin-Hua Piao,2 Akio Asai,2 Akira Yoshida,2 Eiju Tsuchiya,2 Wolfram Ruf,2 and Yohei Miyagi1

1Molecular Pathology and Genetics Division, Kanagawa Cancer Center Research Institute; 2Department of Obstetrics, Gynecology and Molecular Reproductive Science, Yokohama City University Graduate School of Medicine, Yokohama, Japan; 3Department of Neurosurgery, Hirakata Hospital, Kansai Medical University, Osaka, Japan; and 4Department of Immunology, The Scripps Research Institute, La Jolla, California

Abstract
Blood coagulation factor VII (fVII) is physiologically synthesized in the liver and released into the blood. Binding of fVII to tissue factor (TF) at sites of vascular injury triggers coagulation and hemostasis. TF/fVIIa complex formation on the surface of cancer cells plays important roles in cancer biology. Although fVII is synthesized by hepatocellular carcinoma, it remained unclear how TF/fVIIa complex formation and promigratory signaling can occur for most other cancers in extravascular locations. Here, we show by reverse transcription-PCR analysis that nonhepatic cancer cell lines constitutively express fVII mRNA and that endogenously synthesized fVII triggers coagulation activation on these cells. fVII expression in cancer cells is inducible under hypoxic conditions and hypoxia-inducible factor-2α bound the promoter region of the FVII gene in chromatin-immunoprecipitation analyses. Constitutive fVII expression in an ovarian cancer cell line enhanced both migration and invasion. Enhanced motility was blocked by anti-TF antibodies, factor Xa inhibition, and anti–protease-activated receptor-1 antibody treatment, confirming that TF/fVIIa stimulated migration by triggering cell signaling. This study shows that ectopic synthesis of fVII by cancer cells is sufficient to support proinvasive factor Xa–mediated protease-activated receptor-1 signaling and that this pathway is inducible under hypoxia. (Cancer Res 2006; 66(19): 9453-60)

Introduction
Coagulation factor VII (fVII) is the key triggering enzyme of the extrinsic coagulation pathway (1). Tissue factor (TF) is the essential cofactor of fVIIa (1) and is an integral membrane protein that is widely expressed in normal and cancerous tissues in humans. TF triggers a procoagulant state in advanced cancer when tumor cells come in contact with the blood or when TF-positive microvesicles are increasingly shed into the circulation (2). The evidence is increasing that the TF/fVIIa complex also initiates key pathogenic mechanisms in cancer, including angiogenesis (3–6), cell migration and invasion (3, 7), and cell survival (8, 9). Although activation of coagulation is critical for TF-dependent hematogenous cancer metastasis (10), it is likely that TF activities in cancer progression also involve direct cell signaling triggered by TF/fVIIa complex formation on cancer cells.

TF signaling pathways involve, on the one hand, the cytoplasmic domain (3, 5, 7, 11) that regulates cell adhesion and migration (12, 13); on the other hand, the TF/fVIIa complex signals by proteolytic mechanisms (14–17). TF/fVIIa cleaves and activates protease-activated receptor (PAR)-2 to induce these signaling pathways (18, 19), but the TF/fVIIa/factor Xa (fXa) coagulation initiation complex can also signal by activating either PAR-2 or PAR-1 (19).

Most plasma proteins are synthesized in the liver (20). Hepatocytes are the predominant source of fVII production under normal physiologic conditions, although fVII is also expressed by monocytes/macrophages in inflammation (21, 22) and atherosclerosis (23). By Northern blotting of human tissue mRNA, FVII gene expression was only detected in the liver (20), confirming a selective hepatic synthesis under normal conditions. However, fVII is expressed in some hepatocellular carcinoma cells (24, 25), and this ectopic fVII synthesis has been proposed to trigger liver cancer–specific invasion activity mediated by binding of fVIIa to TF pathway inhibitor-2 (26). Among cancers other than hepatocellular carcinoma, TF/fVIIa complex formation has been observed at the invasive edge of bladder cancer (27), ovarian cancer (28), and laryngeal carcinoma tissues (29). However, these studies were conducted by immunohistochemical procedures and the accumulated fVII on the cell surface was assumed to arise from the blood plasma due to extravasation from hyperpermeable blood vessels (27).

In the present study, we show that ectopic expression is frequent in various cancers by analyzing fVIIa mRNA in 46 cancer cell lines by reverse transcription-PCR (RT-PCR) analysis. We further show that endogenous synthesis of fVII by an ovarian cancer cell line is sufficient to promote cell migration and invasion activities of cancer cells. Invasion is one of the important properties of tumor cells that enable escape from hypoxic conditions, especially during active growth (30). Indeed, proinvasive molecules, such as growth factor receptor c-Met, urokinase-type plasminogen activator receptor (31), and Rab11, a vesicular trafficking-associated protein (32), are up-regulated under hypoxia. We further show that ectopic fVII expression is regulated by hypoxia and thus establish a regulatory pathway by which tumor cells become invasive by up-regulation of a promigratory protease-signaling complex.

Materials and Methods
Cells, tissue specimens, and cell culture. A total of 46 human cancer cell lines were used in this study. All the cell lines were cultured in RPMI 1640 supplemented with 10% fetal bovine serum (FBS; Moregate, Brisbane, Australia) at 37°C in a humidified atmosphere under 5% CO2. Hepatoma cell lines HepG2, HLF, HLE, HUH-6 clone 5, HUH-7, and PLC/PRF/5,
gibloblasma cell line T98G, ovarian cancer cells KURAMOCHI, PA-1, and TYK-nu, lung cancer cell lines SBC-2, SBC-3, and SBC-4, and breast cancer cell lines MDA-MB-435 and MDA-MB-231 were obtained from the RIKEN Bioresource Center Cell Bank (Tsukuba, Japan). Gibloblasma cell lines U87, U937, SF126, SF188, and SF763, ovarian cancer cell lines OVSAYO, OVTOKO, OVMANA, OVISE, OVSAGO, and OVKATE, prostate cancer cell lines LNCaP, PC-3, and DU-145, gastric cancer cell line KATOII, MKN28, MKN45, STKM1, and STKM2, and thyroid cancer cell lines KTA1, KTA2, KTA3, KTA4, TTA1, TTA2, and TTA3 were previously described (33–36). Breast cancer cell line Hori was studied in our laboratory. Ovarian adenocarcinoma tissues, subclassified into the common ovarian surface epithelial-stromal tumors, were obtained from surgically removed specimens under the approval of the Ethical Committee of Yokohama City University School of Medicine. Written informed consent was obtained from all patients before the operation.

**Semi-quantitative RT-PCR analysis.** Total RNA (2 µg) was subjected to a reverse transcription reaction and aliquots were used for PCR amplification with Platinum Taq DNA polymerase (Invitrogen, Carlsbad, CA) of TF (28 or 36 cycles), FVII (34 or 42 cycles), γ-glutamylcarboxylase (28 or 36 cycles), PAR-1 and PAR-2 (35 cycles), and β-actin transcripts (30 cycles). The following PCR primers were used: TF, 5'-CTACTGTTCTACTGTTGATACTAAG-3' and 5'-CAAGCTCTGTAGTGTTGACATG-3'; FVII, 5'-GAGTGTCCATGGCAGGTCC-3' and 5'-CAGCGGACGGTCTGGTGTG-3'; γ-glutamyl carboxylase, 5'-CTACAGACCGCTTGGCACAAACG-3' and 5'-CAAGCTCCTGTTGGAACCTGAGTC-3'; β-actin, 5'-ACTCCTTACATGATAGTCT-3' and 5'-TCATGGTTGCTGACCGAGACT-3'.

**Analysis of FVII gene expression induced by hypoxia.** For analyses of FVII gene expression under hypoxic conditions, cancer cells (9 × 10^4) were cultured in 50-mm diameter dishes for 16 hours. The medium was replaced with 5 mL of fresh medium containing 500 µM/L cobalt chloride (CoCl2 Sigma, St. Louis, MO) for 0, 2, 4, 8, 12, 24, and 36 hours, followed by total RNA isolation and RT-PCR analyses. For incubation at 1% O2 condition, cells were cultured in multigas incubator (Juji Field, Inc., Tokyo, Japan). Alternatively, FVII mRNA levels were determined by real-time PCR analysis in a LightCycler (Roche, Indianapolis, IN) using a QuantiTect RT-PCR Kit (Qiagen, Valencia, CA). Monitoring of the PCR amplification of the FVII transcripts was done by fluorescence resonance energy transfer–based detection using hybridization probes labeled with fluorescent dyes (BITC or LC-Red640). The copy numbers of FVII transcripts were determined using the pRES/βII plasmid (described below) as standard. The PCR primers used were 5'-ACCCCAAGGGGGAATTTGTG-3' and 5'-CCACCCAGATGGTGTTGATC-3'; 5'-GAGTGTCCATGGCAGGTCC-3' and 5'-CAAGCTCCTGTTGGAACCTGAGTC-3'; and 5'-ACTCCTTACATGATAGTCT-3' and 5'-TCATGGTTGCTGACCGAGACT-3'.

**Results**

FVII, TF, and γ-glutamyl carboxylase mRNA expressions in cancer cells. We tested 46 cancer cell lines for the FVII gene expression. Semi-quantitative RT-PCR analyses were done using different PCR cycle numbers. As expected, FVII mRNA was detected in some hepatic cancer cells. However, no transcripts were observed in HLE and HLF cells, which are non-differentiated hepatoma cell lines established from a hepatocellular carcinoma

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(Fig. 1A, liver; ref. 42). HepG2, HUH-6/clone 5, and HUH-7 cells had high expression of fVIIa because the transcript was detectable at low-cycle number PCR (Fig. 1A). No transcripts were detected in six brain glioblastoma cell lines even when high-cycle number PCR was done (Fig. 1A, brain). In ovarian, prostate, lung, stomach, and thyroid cancer cell lines, fVII mRNA levels were high in some cell lines at low cycle number, but in general, fVII was only detected with high-cycle number PCR (Fig. 1A). Expression of fVII mRNA in KURAMOCHI and KATOIII cells seemed to be similar to that in hepatic cancer cells. On the other hand, high levels fVII mRNA expression were observed in most of the breast cancer cell lines (Fig. 1A, breast) with the highest expression levels observed in YMB-1, MDA-MB-453, and MCF-7 cells.

To exclude that ectopic fVII expression is an artifact of in vitro culture, we also tested surgical specimens of ovarian cancer and found that most of them expressed fVII transcripts (Fig. 1B). In addition, we examined mRNA expressions of TF, the receptor and obligatory cofactor for fVIIa in these samples. TF was expressed in all cancer cells and, typically, high fVII-expressing cells also showed high levels of TF mRNA (Fig. 1). fVII is a vitamin K–dependent protein that requires posttranslational γ-carboxylation of specific glutamic acid residues in its NH₂ terminus for coagulant activity (43). All cancer cells and ovarian cancer isolates expressed γ-glutamyl carboxylase, the crucial vitamin K–dependent enzyme, indicating that proper posttranslational modification of ectopically expressed fVII is possible.

Hypoxic stress up-regulates fVII mRNA expression by recruiting HIF-2α/EPAS-1 to the FVII promoter. Proinvasive cancer cells are frequently subjected to hypoxic stress and adapt to this condition by up-regulation of protective cellular mechanism (44). We tested whether cancer cells with no or low fVII mRNA expression could up-regulate fVII in response to hypoxic stress and thus increase proinvasive potential. Three nonhepatic cancer cells were exposed to CoCl₂, known to induce hypoxic stress, and fVII mRNA expression was monitored by RT-PCR over time. Ovarian cancer cells (OVSAHO and OVSAYO) showed a time-dependent up-regulation of fVII mRNA levels with a peak at 8 hours (Fig. 2A). Figure 2B confirms by quantitative real-time RT-PCR the substantial expression.

Figure 1. RT-PCR analyses of fVII, TF, and γ-glutamyl carboxylase (GGCX) mRNA expressions in 46 cancer cell lines (A) and 9 ovarian cancer surgical specimens (B). The numbers on the right side of each lane indicate the numbers of PCR cycles. β-Actin expression was used as an internal standard.
up-regulation of FVII mRNA expression under hypoxic stress in OVSAYO and the gastric cancer cell line MKN28 (Fig. 2B). We confirmed the up-regulation of FVII transcription in OVSAYO cells under actual 1% O2 condition although the amplitude of the induction was smaller than that caused by CoCl2 treatment (Fig. 2B).

Hypoxia stabilizes HIF protein levels and thus induces HIF-dependent transcriptional responses under hypoxic conditions (44). HIF-1α and HIF-2α (also known as EPAS-1) bind to hypoxia-responsive elements within gene promoters and play crucial roles as transcriptional factors. We used chromatin immunoprecipitation analyses to test whether HIFs bind to the promoter regions of the FVII and VEGF genes in OVSAYO or MKN28 cells. Representative of multiple chromatin immunoprecipitation experiments using isolated nuclei or intact cells for cross-linking and typical results using isolated nuclei (OVSAYO cells) and intact cells (MKN28 cells). Straight arrows, three regions amplified by PCR. Bent arrows, transcription start site. M, 100-bp marker ladder. I, input PCR control using DNA prepared from sonicated chromatin without immunoprecipitation. N and H, results for normoxia (cultured without CoCl2 treatment) and hypoxia induced by CoCl2 treatment, respectively.

The second, more distant region was located ~600 bp upstream of the FVII promoter region and contained a single hypoxia-responsive element sequence (5’-GACGTG-3’). We confirmed these promoter sequences in OVSAYO cells by DNA sequencing (data not shown). As a positive control for the HIF-binding activities, we used the promoter region of the VEGF gene, to which HIF-1α and HIF-2α bind in response to hypoxia. HIF-1α and HIF-2α were immunoprecipitated from total OVSAYO cells or isolated OVSAYO cell nuclei. Chromatin immunoprecipitation assay showed the expected binding of HIF-1α or HIF-2α/EPAS-1 with the promoter region of the VEGF gene (Fig. 2D). No binding of HIF-1α was detected to the two chosen regions of the FVII gene under hypoxic stress (Fig. 2D). In contrast, HIF-2α was found to bind to the promoter, but not the more distant upstream region of the FVII gene in response to hypoxic conditions (Fig. 2D). The depicted results with anti-HIF-2α antibody NB100-122 were confirmed by chromatin immunoprecipitation using another anti-HIF-2α antibody (NB100-132; data not shown). Similar results were obtained when MKN28 cells (Fig. 2D) or isolated MKN28 cell nuclei (data not shown) were used for chromatin immunoprecipitation analyses. Thus, HIF-2α binding to the FVII promoter was specifically induced by hypoxic stress.
Ectopically synthesized fVIIa is functionally active and involved in cell migration and invasion. To investigate whether the fVII gene expression in nonhepatic cancer cells leads to formation of a functional TF/fVIIa complex on the surface of cancer cells, we tested whether TF/fVIIa on fVII gene-expressing breast cancer cell line YMB-1 and gastric cancer cell line KATOIII can activate fX (Fig. 1A). Real-time RT-PCR showed that YMB-1 cells expressed fVII mRNA at comparable levels (≈70%) to HepG2 hepatocellular carcinoma cells. We also examined MKN28 cells, a non-fVII-expressing gastric cancer cell line with significant TF expression (Fig. 1), as a negative control. Both YMB-1 cells (Fig. 3A) and KATOIII cells (Fig. 3A) showed considerable fXa generation (6.5 and 3.6 pmol/L/min, respectively), but no activity was detected with fVII-negative MKN28 cells (Fig. 3A). fXa generation was also undetectable with OVSAYO cells, which expressed very low levels of fVII (Fig. 3A). fXa generation on YMB-1 or KATOIII cells was diminished (to 0.44 and 1.1 pmol/L/min, respectively) when the activity of the TF/fVIIa complex was blocked with the potent inhibitory antibody TF 5G9 (Fig. 3A). These results show that endogenous expression of fVII by tumor cells is sufficient to form a procoagulant TF/fVIIa complex on the tumor cell surface.

We next tested whether formation of the TF/fVIIa complex on fVII-expressing tumor cells enhances cell migration and/or invasion. Transwell analysis using a highly fVII-expressing breast cancer cell line (MDA-MB-453) revealed that the number of migrated or invaded cells was diminished when cells were treated with anti-TF antibody TF 5G9 (Fig. 3B), suggesting that ectopically expressed TF/fVIIa increases cell migration and invasion.

Effects of ectopic fVII expression on migration and invasion of ovarian cancer cells. To clearly show that ectopic expression is...
sufficient to enhance cell migration and/or invasion, we stably transfected OVSAYO cells that had very low levels of fVII expression and minimal TF/fVIIa activity on the cell surface. Two independent clones that expressed fVII (designated OVSAYO/fVII.2 and OVSAYO/fVII.16) and two vector control clones (designated OVSAYO/IRES.1 and OVSAYO/IRES.5) were established. By Western blotting, fVII was secreted into the conditioned media of both OVSAYO/fVII.2 and OVSAYO/fVII.16 cells, but no fVII was detected in the vector control clones (Fig. 3C). Real-time RT-PCR analysis showed 6- to 7-fold higher fVII mRNA expression levels in OVSAYO/fVII.2 and OVSAYO/fVII.16 cells relative to HepG2 cells. Both OVSAYO/fVII.2 and OVSAYO/fVII.16 clones showed strong fXa generation (107 and 101 pmol/L/min, respectively) whereas vector control clones did not activate coagulation (Fig. 3A). Transwell migration assays showed that ectopic expression of fVII induced a 3- to 4-fold increase in the number of migrating cells (Fig. 3D). Ectopic fVII expression also enhances cell invasion through Matrigel by 4- to 6-fold compared with the non-fVII-expressing cells (Fig. 3D). To confirm that migration is enhanced by formation of a TF/fVIIa complex on the tumor cell surface, antibody inhibition experiments were done. A combination of antibodies (6B4 and 9C3) that is known to efficiently block fVIIa binding to TF suppressed migration and invasion to levels observed with cells that were not transfected with fVIIa. The antibodies did not suppress migration of cells that did not express fVII, further showing specificity (Fig. 4A and B). However, migration and invasion were also suppressed by an antibody (5G9) that has little effect on TF/fVIIa complex formation. This antibody is known to block binding of Fx to TF/fVIIa and thus abolishes fXa dependent signaling (19). However, this antibody also blocks coagulation activation and thrombin generation that may have stimulated migration in the assay that was done in the presence of serum.

**Ectopic expression of fVIIa enhances migration and invasion through fXa-dependent cell signaling.** To distinguish between signaling of the TF/fVIIa/fXa complex and downstream thrombin generation, we used specific inhibitors of fXa and thrombin. Transwell assays in the presence of a potent fXa inhibitor, NAP-5, showed a 3- to 5-fold reduction in the numbers of migrating or invading OVSAYO/fVII.2 or OVSAYO/fVII.16 cells (Fig. 4C and D, dotted columns). However, the potent thrombin inhibitor hirudin had no effects on migration or invasion (Fig. 4C and D, bars).
and D, black columns). Thus, FXa-dependent signaling is responsible for stimulated migration in cells that ectopically express FVIIa. The ternary TF/FVIIa/Xa complex can activate both PAR-1 and PAR-2 in a FXa-dependent manner (19). RT-PCR showed that PAR-1 and PAR-2 were expressed in OVSAYO/FVII2 cells, similarly to the parental OVSAYO cells (Fig. 5A). Anti-PAR-1 treatment significantly reduced (50-70%) migration of VII-expressing ovarian cancer cells (Fig. 5B, black columns). Cleavage blocking anti-PAR-2 antibody produced little (10-20%) inhibition of cell migration (Fig. 5B, dotted columns) and a slight additive inhibitory effect was seen when cells were pretreated with both anti-PAR-1 and anti-PAR-2 antibodies (Fig. 5B, hatched columns). Thus, in ovarian cancer cells, PAR-1 cleavage plays an essential role in TF/FVIIa–induced motility.

Discussion

In this study, we provide novel evidence that ectopic expression of FVII is frequent in cancer cells of different origin. The notable exception was glioblastoma in which no FVII transcript was detected in any of the established cell lines analyzed. In addition, we show that FVII-expressing cells invariably express the FVII cellular receptor, TF, and γ-glutamyl carboxylase, the key enzyme for requisite posttranslational modification of FVIIa. Consistently, ectopically expressed FVIIa was functional on the surface of cancer cells to form a TF/FVIIa complex that triggered FXa generation. In previous studies, FVII was found to be associated with TF-positive tumor cells (27–29). Our data challenge the concept that FVII is derived from the circulating blood plasma to associate with tumor cells and introduce the regulated ectopic expression of FVIIa by tumor cells as a potentially novel pathogenetic factor that promotes cancer cell migration and invasion.

Ectopic FVII expression was further shown to be regulated by hypoxic conditions. We show hypoxia-induced association of HIF-2α, but not HIF-1α, with the FVII promoter. Under the same conditions, both HIF-1α and HIF-2α were found to associate with the promoter of the VEGF gene, further showing the specificity of the differential binding of HIFs to the FVII gene promoter. The fact that the relevant the FVII promoter region contains HIF-1 ancillary sequences, but not a typical hypoxia-responsive element, may be the underlying cause for the selective binding of HIF-2α. It is of interest that glioblastoma cells have recently been shown to up-regulate TF expression in hypoxia (2). Thus, cancer cells may use the regulation of either TF or FVIIa as a mechanism to adjust to a changing tumor microenvironment. In addition, it is worth considering that ectopic synthesis of FVII by hypoxic nonmalignant cells could play a role in TF-dependent angiogenesis and tissue regeneration.

We found that ectopic synthesis of FVII was sufficient to drive the migration and invasion of breast and ovarian cancer cells in transwell analyses. These activities of ovarian cancer cells were profoundly inhibited by FXa, but not by a thrombin inhibitor. In the transwell assay, FX is present in the serum as a chemoattractant stimulus. On the TF/FVIIa–expressing tumor cell surface, FX is then likely activated to enhance migration. In addition, we show that PAR-1 is the central signaling receptor responsible for FXa-enhanced motility. In vivo, FX may be produced ectopically by cancer cells. We detected very weak FX mRNA expression in OVSAYO cells by RT-PCR, which seemed to be insufficient to stimulate migration (data not shown). However, FX protein is frequently detected in cancer specimen (46) and may be locally delivered by stromal cells. For example, macrophages can bind FX through Mac-1 (47) and may locally deliver FX to the tumor microenvironment.

For breast cancer cells, it is controversial whether the TF/FVIIa complex by signaling through PAR-2 (48) or the ternary TF/FVIIa/Xa complex predominantly stimulates migration (49). In our ovarian cancer model with endogenously synthesized FVIIa, the predominant proinvasive stimulus comes from exogenous FX, rather than FVIIa. It is tempting to speculate that endogenous, regulated FVII expression enables the tumor cells to specifically control the interactions with host cells and respond to a changing microenvironment. Ectopic expression of FX, as shown for various ovarian and breast cancer cells, may sensitize the tumor cells to respond to promigratory and proinvasive cues, such as extravasated FX. This sensitization will likely select tumor cells to escape from hypoxic environments and thus represents a key factor of malignant tumor progression and metastasis.

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