The antigenic binding sites of autoantibodies to factor XII in patients with recurrent pregnancy losses

Akifumi Inomo*, Toshitaka Sugi*, Yoshihito Fujita, Hidehiko Matsubayashi, Shun-ichiro Izumi, Mikio Mikami
Department of Obstetrics and Gynecology, Specialized Clinical Science, Tokai University School of Medicine, Kanagawa, Japan

Summary
Recently, numerous studies have suggested an association between factor XII (FXII) deficiency and recurrent pregnancy losses, and between autoantibodies to FXII and recurrent pregnancy losses. Autoantibodies to FXII rather than FXII deficiency may be a risk factor for recurrent pregnancy losses. To know the pathogenesis of autoantibodies to FXII, epitope mapping study was done. Seventeen anti-FXII antibody positive recurrent pregnancy loss patients were chosen for this study. We used synthetic peptides in inhibition and direct binding studies to identify the antigenic binding site of autoantibodies to FXII. Among plasmas from 17 recurrent pregnancy loss patients who were positive for autoantibodies to FXII, 13 patients (76.5%) recognized amino acids 1–30, the amino-terminal heavy chain region that is known as factor XII binding site to platelet glycoprotein Ibα.

Keywords
Recurrent pregnancy losses, factor XII, kininogen, kalikrein-kinin system, antiphosphatidylethanolamine antibody, platelet

Thromb Haemost 2008; 99: 316–323

Introduction
Deficiencies of contact proteins such as factor XII (FXII) and high-molecular-weight kininogen are not associated with clinical bleeding despite marked prolonged activated partial thromboplastin time (aPTT), a surface-activated coagulation protein screening test. Paradoxically, studies suggest that contact proteins have anticoagulant, profibrinolytic functions in a physiologic milieu, on endothelial cells (1–6). Numerous clinical studies suggest that contact protein deficiencies may be associated with impaired contact factor-dependent fibrinolysis. This result may contribute to an increased incidence of thrombosis in patients with congenital FXII deficiency, an increased incidence of FXII deficiency in patients with venous thrombosis, and acquired thrombotic disorders such as myocardial infarction and re-thrombosis of coronary arteries after thrombolytic therapy (5–8). However, other studies suggest that FXII plays no role in ischemic vascular disease (9). Thus, it is unclear from existing literature whether a factor deficiency leads to thrombophilia.

Recently, numerous studies have suggested an association between contact protein deficiencies and recurrent pregnancy losses (10–12), and between autoantibodies to contact proteins and recurrent pregnancy losses (13, 14). Sugi and McIntyre (14) reported that certain antiphosphatidylethanolamine antibodies (aPE) are not specific for phosphatidylethanolamine (PE) per se, but are directed to PE-binding plasma proteins, kininogens. Sugi et al. tested recurrent pregnancy loss patients for aPE, especially those patients who lose during the embryonic period (<10 weeks' gestation). They showed a strong association between recurrent pregnancy loss and aPE, the latter of which requires the presence of kininogen or other plasma proteins (15, 16). In this study, 90.5% of the patients who were positive for plasma protein-dependent IgG aPE were kininogen-dependent. These data suggest that aPE may therefore represent a significant risk factor for early recurrent pregnancy loss.

Schved et al. (10) reported the cases of three young women with a FXII deficiency (two homozygous and one heterozygous) and a clinical history of spontaneous abortion. Braulke et al. (11) reported on eight patients with moderately reduced level of FXII found among 43 patients with repeated abortions. Recently, Gris et al. (12) reported the prevalence of haemostasis abnormalities in 500 unexplained primary recurrent aborters. They found 9.4% of the patients with an isolated FXII deficiency. Gallimore et al. (17) reported a high incidence (20.9%) of apparently true FXII deficiency in patients who were lupus anticoagulant (LA) positive. They have hypothesized that antibodies to FXII might be present in some patients who are LA positive and that immune complexes may be formed leading to reduced levels of FXII.
They studied plasma samples from LA positive patients for the presence of antibodies to FXII and reported that many patients were positive for antibodies to FXII detected by ELISA and surface plasmon resonance (18). Jones et al. (19) reported that when levels of FXII were compared in patients with and without antibodies to FXII, significantly lower levels of FXII were seen in patients with antibodies to FXII. This suggests that the immune complex formation and subsequent sequestration resulted in reduced levels of FXII. They also reported that antibodies to FXII showed a strong and statistically significant association with recurrent fetal loss (odds ratio [OR] 5.4, p = 0.025) (20). Autoantibodies to FXII rather than FXII deficiency may be a risk factor for thromboembolism and recurrent pregnancy losses.

In the present study, we used synthetic peptides in inhibition and direct binding studies to identify the antigenic binding sites of autoantibodies to FXII in patients with recurrent pregnancy losses.

Materials and methods

Sources of peptides

Peptides were synthesized at the Laboratory for Molecular Science Research, Tokai University School of Medicine. These peptides were synthesized on a PSSM-8 synthesizer (Shimadzu, Tokyo, Japan). The peptides were purified by preparative high performance liquid chromatography (HPLC) on a SynProPep cartridge system using reverse phase C18 columns (PepRPC18 column, Shimadzu). An amino acid sequence analysis was carried out using an automated protein/peptide sequencer, PPSQ-21 A system (Shimadzu). Nine overlapping and sequential peptides of 24-31 residues in length were synthesized to span the amino-terminal heavy chain region (Ile1-Ala158) of FXII: peptides IPP30, EPC30, PFQ30, HKC31, DQD30, HCS24, PCQ30, KCF31 and WYR28 (Table 1).

Patients

Blood samples were obtained with informed consent from 197 patients with recurrent pregnancy losses. Patients with recurrent pregnancy losses had two or more pregnancy losses before 10 weeks gestation, exclusive of ectopic pregnancy and/or elective abortion. All patients were evaluated by hysterosalpingography, vaginal ultrasound, karyotypes of both partners, endocrine monitoring (prolactin, thyroid function, fasting blood sugar, luteal phase progesterone), infectious factors (group B streptococcal and Chlamydia trachomatis infection), and autoantibodies (lupus anticoagulant, anticardiolipin, antiphosphatidylserine, antiphosphatidylethanolamine, antinuclear antibodies, and anti-FXII antibodies). Anti-FXII antibodies were detected by the immunoblot. Seventeen previously determined anti-FXII antibody-positive patients with recurrent pregnancy loss were chosen for this study. The mean age of the patients was 34 years (range 26-41), and the mean number of pregnancy losses was 3.1 (range 2-4). Six, three and three of 17 patients each were positive for aPPE, antiphosphatidylserine and anticardiolipin antibodies, respectively. Eight of 17 patients were negative for any antiphospholipid antibodies. No patients fulfilled criteria for definite antiphospholipid syndrome. FXII activities of 17 patients were 85.1 ± 38.3%. FXII activities of eight patients were less than 60%. All plasma samples were stored at -70°C until use.

SDS-PAGE and immunoblot

SDS-PAGE was done in 8% homogenous resolving gels and 3% stacking gels. Factor XIIa (Enzyme Research Laboratories, South Bend, IN, USA) was boiled for 2 minutes (min) in 2% SDS containing 0.1M Tris/HCl, pH 6.8, 20% glycerol and 0.2% bromophenol blue. Transfer to nitrocellulose membrane was done overnight at 0.1 amps. Membranes were blocked for 1 h (h) with 1% bovine serum albumin (BSA) in phosphate-buffered saline (PBS), pH 7.3. Incubation with goat polyclonal antibodies (PoAB) to human factor XII (Enzyme Research Laboratories) or patient plasma (1/100) was done for 1 h followed by three washes with 0.03% Tween 20/PBS. The membrane was exposed to alkaline phosphatase conjugated goat antimouse and/or monoclonal antibodies (MoAb) to human IgG for 1 h followed by washing as above. Using paranitrophenylphosphate buffer, the immunobands were developed.

Purification of IgG from plasmas

IgG was purified from plasmas by diethyl aminoethyl (DEAE)- Sepharose (Pharmacia LKB Biotechnology AB, Upsala, Sweden) followed by proein G-Sepharose (Pharmacia) chromatography. Plasma (1 ml) previously dialyzed in 20 mM Tris/HCl,
pH 7.4, was applied to the DEAE-Sepharose column (1 x 10 cm) equilibrated with 20 mM Tris/HC1, pH 7.4, and washed with the equilibration buffer at a flow rate of 20 ml/h. The effluent from the DEAE-Sepharose column was applied to a protein G-Sepharose column (5 ml) equilibrated with 20 mM Tris/HC1, pH 7.4. After washing with buffer, protein G-bound IgG was eluted with a 0.2 M glycine/HC1 buffer, pH 3.0, and immediately neutralized with saturated Tris and dialyzed against Tris-buffered saline (TBS; 0.02 M Tris, 0.15 M NaCl, pH 7.3).

Mapping of the anti-FXII antibody epitope
Synthetic peptides covering the sequence of the amino-terminal heavy-chain region of FXII were examined for their reactivity with anti-FXII antibodies. Sumilon microtiter plates (Sumitomo Bakelite, Tokyo, Japan) were coated overnight at 4°C with 100 µl of a 10 µM solution of the respective peptide in TBS. Each well was blocked for 1 h with 3% BSA in TBS containing 0.02% Tween 20 (Sigma) followed by incubation with 100 µl of anti-FXII antibody positive patient plasma diluted 1:100 or purified IgG (37.5 µg/ml) from patient plasma in 1% BSA/TBS containing 0.03% Tween 20 for 1 h. Alkaline phosphatase conjugated MoAb to human IgG (Sigma, St. Louis, MO, USA) was added, followed by the addition of substrate solution. The plates were washed three times with TBS containing 0.03% Tween 20 after peptide coating, blocking, serum and conjugate incubations. After color development produced by paranitrophenyl phosphate substrate, the optical density (OD) at 405 nm was measured. Color development was stopped with 75 µl of 3N NaOH when the OD of a positive control reached 1.0.

Inhibition of anti-FXII antibody binding to IPP30 by peptides
Sumilon plates were coated overnight at 4°C with 100 µl of a 10 µM solution of the IPP30 in TBS. Each well was blocked for 1 h with 3% BSA in TBS containing 0.03% Tween 20 (Sigma). Synthetic peptides IPP30 and HCS24 (1.5625, 3.125, 6.25, 12.5, 25, 50, or 100 µM) were incubated with 100 µl of anti-factor XII antibody-positive patient plasma (X) diluted 1:200 in 1% BSA/TBS containing 0.03% Tween 20 for 1 h. Alkaline phosphatase conjugated MoAb to human IgG (Sigma) was added followed by the substrate solution. The plates were washed three times with TBS containing 0.03% Tween 20 after peptide coating, blocking, serum and conjugate incubations. After color development produced by paranitrophenyl phosphate substrate, the OD at 405 nm measured.

Results
Anti-FXII antibody detection by immunoblot
FXIIa was subjected to SDS-PAGE. The slab gel contents were transferred to nitrocellulose then immunoblotted with patient plasmas. All seventeen previously determined anti-FXII antibody positive recurrent pregnancy loss patients recognized FXIIa whole molecule under non-reducing conditions and many of them recognized heavy chain of FXII under reducing conditions (Fig. 1). No patient recognized the light chain of FXII.

Direct binding of anti-FXII antibodies to synthetic peptides
Nine overlapping and sequential peptides of 24–31 residues in length were synthesized to span the amino-terminal heavy chain region (Ile 1- Ala 159) of FXII: peptides IPP30, EPC30, PPQ30, HKC31, DQQ30, HCS24, PCQ30, KCF31 and WYR28 (Table 1). These peptides cover the several structural domains, i.e. starting from the amino-terminus, a fibronectin domain type II, an epidermal growth factor-like domain, a fibronectin domain type I. These domains contain candidate sites for surface-binding regions or cell-binding regions of FXII such as amino acid

![Figure 1: A representative experiment showing patient antibody binding to factor XIa whole molecule and heavy chain of factor XII. Factor XIa was subjected to SDS-PAGE under nonreducing (NR) and reducing (R) conditions. Immunoblots with polyclonal antibodies (PoAb) to FXII, normal plasma (control) or anti-factor XI antibody positive patient plasmas. HC: heavy chain, CL: light chain.](image-url)
Table 2: Binding of anti-factor XII antibodies to synthetic peptides in patients X. ELISA was performed using microtiter plates coated with 10 µM of the respective peptide. In control wells, no peptide was coated and only TBS was incubated. IgG anti-factor XII antibody-positive patient plasma X (1:100) was applied in triplicate wells followed by an alkaline phosphatase-conjugated secondary antibody. The absorption was measured at 405 nm. A plasma was considered positive if the difference between the OD in the ELISA with peptide and in the ELISA with control TBS was greater than 0.3.

<table>
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<tr>
<th>IPP30</th>
<th>EPC30</th>
<th>PFQ30</th>
<th>HKC31</th>
<th>DQD30</th>
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<td>1.064 ± 0.015</td>
<td>0.49 ± 0.009</td>
<td>0.473 ± 0.03</td>
<td>0.623 ± 0.013</td>
<td>0.493 ± 0.012</td>
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<tr>
<td>HCS24</td>
<td>PCQ30</td>
<td>KCF31</td>
<td>WYR28</td>
<td>TBS</td>
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<tr>
<td>0.411 ± 0.024</td>
<td>0.536 ± 0.024</td>
<td>0.457 ± 0.01</td>
<td>0.443 ± 0.005</td>
<td>0.45 ± 0.005</td>
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OD (mean ± SD).

residues 1–28, 39–47 and 134–153. These peptides were designed not to cause conformational changes in each domain by breaking internal disulfide loops. For example, peptide EPC30 (25–55) contains a fibronectin domain type II that has a disulfide bond between Cys28 and Cys54. Likewise, HCS24 (78–101) covers the epidermal growth factor-like domain, which has a disulfide bond between Cys80 and Cys92.

These nine peptides were examined for their reactivity with anti-FXII antibodies. ELISA was employed using microtiter plates coated with 10 µM of the respective peptide. IgG anti-factor XII antibody-positive patient plasma or normal control plasma (1:100) was applied followed by an alkaline phosphatase-conjugated secondary antibody. The absorption at 405 nm was measured. A plasma was considered positive if the difference between the OD in the ELISA with peptide and in the ELISA with control was greater than 0.3. This value was based on the evaluation of 41 normal individuals for direct binding to synthetic peptides by ELISA. From these data, the number of multiples of the median that accounted for 95% of this normal population ELISA values was 2.9. The OD associated with 2.9 multiples of the median was 0.234. To ensure the values were not borderline, 0.234 was rounded off to 0.3.

Figure 2: Binding of anti-factor XII antibodies to synthetic peptides. A) Increasing concentrations of synthetic peptide IPP30 was coated on microtiter plate wells. IgG anti-factor XII-positive patient plasma (X) or normal control plasma (1:100) was applied followed by an alkaline phosphatase-conjugated secondary antibody. The absorption at 405 nm was measured. B) Increasing concentrations of synthetic peptide IPP30 or HCS24 were coated on microtiter plate wells. Purified IgG (37.5 µg/ml) from patient X or normal control was applied followed by an alkaline phosphatase-conjugated secondary antibody. The absorption at 405 nm was measured.
Among the 17 recurrent pregnancy loss patients who were positive for anti-FXII antibodies, plasma from 13 patients (76.5%) recognized the IPP30 peptide, which encompasses the cell-binding sequences and surface-binding regions. Three patient plasmas (17.6%) recognized HKC31. Four patient plasmas (23.5%) recognized none of nine peptides.

Among 10 recurrent pregnancy loss patients who recognized only the IPP30 peptide, patient X was chosen for the dose-dependent and inhibition studies. This patient had a high titer of IgG anti-FXII antibody that recognized IPP30, but did not recognize eight other peptides (EPC30, PFQ30, HKC31, DQD30, HCS24, PCQ30, KCF31 and WYY28) (Table 2).

**Binding of anti-FXII antibodies to synthetic peptide, IPP30**

Increasing concentrations (0.3125, 0.625, 1.25, 2.5, 5, 10, 20 μM) of synthetic peptide IPP30 was coated onto microtiter plate wells. IgG anti-factor XII antibody-positive patient plasma (X), normal control plasma (1:100), purified IgG from patient X or normal control (37.5 μg/ml) was applied followed by an alkaline phosphatase-conjugated secondary antibody. The absorption at 405 nm was measured. As shown in Figure 2, anti-FXII antibodies bound to IPP30 in a concentration-dependent manner.

Synthetic peptide IPP30 (10 μM) was coated on microtiter plate wells. Several dilutions (1:6,400, 1:3,200, 1:1,600, 1:800, 1:400, 1:200, 1:100, 1:50) of IgG anti-FXII antibody-positive patient plasma (X) or normal control plasma were applied followed by an alkaline phosphatase-conjugated secondary antibody. Likewise, several concentrations of purified IgG from patient X or normal control were applied followed by a secondary antibody. Absorption at 405 nm was measured. Anti-FXII antibodies were observed to bind to IPP30 in a concentration-dependent manner (Fig. 3).

**Inhibition of anti-FXII antibody binding to IPP30 by peptides**

The plasma from a IgG anti-FXII antibody-positive patient (X) (1:200) was incubated with increasing concentrations (1.5625, 3.125, 6.25, 12.5, 25, 50, 100 μM) of synthetic peptide IPP30 or control peptide, HCS24 in microtiter plate wells that were coated with 10 μM of the IPP30. As shown in Figure 4A, IPP30 blocked anti-FXII antibody binding to IPP30 in a concentration-dependent manner.

Purified IgG (37.5 μg/ml) from patient X or normal control was incubated with synthetic peptide IPP30 (50 μM) in microtiter plate wells that were coated with 10 μM of the IPP30. As shown in Figure 4B, IPP30 blocked anti-factor XII antibody binding to IPP30.

![Figure 3: Dose-dependent anti-factor XII antibody-binding to synthetic peptides.](image-url)

A) Synthetic peptide IPP30 (10 μM) was coated on microtiter plate wells. Several dilutions of IgG anti-factor XII antibody-positive patient plasma (X) or normal control plasma were applied followed by an alkaline phosphatase-conjugated secondary antibody. The absorption at 405 nm was measured. B) Synthetic peptide IPP30 or HCS24 (10 μM) was coated on microtiter plate wells. Several concentrations of purified IgG from patient X or normal control were applied followed by an alkaline phosphatase-conjugated secondary antibody. The absorption at 405 nm was measured.
Figure 4: Inhibition of anti-factor XII antibody-binding to IPP30 by peptides. A) IgG anti-factor XII antibody-positive patient (X) plasma (1:200) was incubated with increasing concentrations of synthetic peptide IPP30 or HCS24 as control in microtiter plate wells that were coated with 10 µM of the IPP30. B) Purified IgG (37.5 µg/ml) from patient X or normal control was incubated with synthetic peptide IPP30 (50 µM) in microtiter plate wells that were coated with 10 µM of the IPP30.

Discussion

Although some studies have identified FXII deficiency as a risk factor for recurrent pregnancy loss (10–12), others failed to find such a relationship (21). Recently, Pauer et al. generated mice deficient for FXII using a gene targeting approach (22). Homozygous FXII-knockout mice showed no FXII plasma activity and had a markedly prolonged aPTT. Interestingly, they reported that matings of FXII+/− males and FXII+/− females resulted in normal litter sizes demonstrating that total FXII deficiency in FXII−/− females does not affect pregnancy outcome (22). Iwaki et al. also reported that in female mice homozygous for a total FXII deficiency, normal deliveries occurred with normal litter sizes (23). In contrast, Jones et al. reported that antibodies to FXII showed a strong and statistical significant association with recurrent fetal loss (OR 5.4, p=0.025) (20). They reported that when levels of FXII were compared in patients with and without antibodies to FXII, significantly lower levels of factor XII were seen in patients with antibodies to FXII (19). This suggests that the immune complex formation and subsequent sequestration resulted in reduced levels of FXII. Autoantibodies to FXII rather than FXII deficiency may be a real risk factor for recurrent pregnancy losses.

HK inhibits thrombin-induced platelet aggregation by inhibiting the binding of thrombin to platelets (24). Domain 3 of HK is responsible (25). Recently, the binding site on platelets, which mediates this effect, was shown to be glycoprotein (GP) Ib-IX complex (26). It has been reported that HK and FXII compete for the same binding site on endothelial cells (27). Bradford et al. reported that FXIIa also inhibits thrombin interaction with platelets in a mechanism also involving binding to the same receptor (28). HK and FXII both directly bind to glycocalcin, the extra cellular subunit of GP Ibα, in a Zn2+-dependent manner. They also reported that FXII binding to platelets was inhibited by monoclonal antibody B7C9, whose non-contiguous epitopes have been mapped to amino acids 1–28 and an icosapeptide in the “finger region” of FXII (29). Interestingly, our present study demonstrates that among plasmas from 17 recurrent pregnancy loss patients who were positive for autoantibodies to FXII, 13 patients (76.5%) recognized amino acids 1–30. This suggests that autoantibodies to FXII in patients with recurrent pregnancy losses may inhibit FXII binding to platelets and may cause pregnancy loss.

The kininogens can inhibit platelet aggregation induced by thrombin. Domain 3 of the kininogen heavy chain was found to inhibit thrombin from binding to the platelet thrombin receptor.
By using specific monoclonal antibodies, Jiang et al. showed that it is the domain 3 region that is responsible for the inhibition of thrombin binding to platelets (25). Kunapuli et al. found that recombinant domain 3 inhibited thrombin-induced platelet aggregation (30). Sugi and McIntyre (14) reported that certain aPE are not specific for PE per se, but are directed to PE-binding plasma proteins, kininogens. Several studies report strong association of aPE with thrombosis and recurrent pregnancy losses (15, 16, 31). Sugi and McIntyre hypothesized that when bound by aPE, the platelet-kinogen complex may no longer render the platelet refractory to thrombin activation, thus predisposing to aggregation and thrombosis. Their in-vitro data (32) support these observations as they demonstrated that kinogen-dependent IgG-aPE purified from several aPE-positive patient plasma caused marked augmentation of thrombin-induced platelet aggregation, but did not affect ADP-induced platelet aggregation. Moreover, kinogen-independent IgG-aPE did not affect thrombin-induced platelet aggregation. For this to occur, it is possible that aPE may recognize the domain 3 region of kinogens subsequent to their binding platelet. Herwald et al. (33) reported that a monoclonal antibody to domain 3, HKH15, which interferes with the complex formation between kinogen and papain, also blocked the cell binding of kinogen and was directed to the extreme carboxy-terminal portion of domain 3. The epitope of HKH15, which binds to domain 3 and blocks the binding of kinogens to platelets and endothelial cells, was mapped using synthetic peptides, which span the entire domain 3 sequence. They reported that one peptide, LDC27, specifically bound to HKH15. Fine mapping of the epitope of HKH15 has also revealed a minimal 3-residue segment in LDC27, named CNA13, to be the antibody-binding site. Katsunuma et al. (34) reported that among plasmas from 24 recurrent pregnancy loss patients who were positive for kinogen-dependent IgG-aPE, 17 (70.8%) recognized the LDC27 peptide. They mapped the aPE-binding region to domain 3 using a plasma specimen from a patient with recurrent pregnancy loss. Interestingly, the aPE of a patient recognized CNA13, which is identical to the epitope of HKH15, Leu331-Met357 (LDC27) and Cys333-Lys345 (CNA13) are located on the carboxy-terminal portion of kinogen domain 3, which is known as the major kinogen heavy-chain cell attachment site where it overlaps its cysteine protease inhibitory region. Because aPE interferes with the balance of haemostasis in vitro, aPE may therefore induce a similar condition in patients thereby causing thrombosis and recurrent pregnancy losses.

Many patients with recurrent pregnancy losses have both FXII deficiency and aPE. In FXII-deficient patients with recurrent pregnancy losses, 32.4% were positive for aPE (T. Sugi, unpublished data). From our epitope mapping studies, both autoantibodies to FXII and kinogen-dependent aPE may block FXII- and kinogen-binding to GP Ib-IX-V complex and augment thrombin-induced platelet aggregation. Thus autoantibodies to FXII and kinogen may cause thrombosis and recurrent pregnancy losses.

Recently, Harris et al. reported the antigenic binding site(s) of antibodies to FXII associated with the antiphospholipid syndrome (35). They investigated plasma samples from 12 female patients with definite antiphospholipid syndrome for the presence of antibodies to FXII. To investigate the antigenic binding site(s) of FXII, 150 peptides of the known FXII sequence were synthesized. Seven patients positive for FXII antibodies were chosen, and each patient's purified IgG or IgM was tested against each peptide. Plasma from only one of the seven patients showed binding to the synthetic peptides. In this patient, two regions were identified as possible antigenic binding site(s) for FXII antibodies: one in the growth factor domain and the other in the catalytic domain. There was no convincing explanation how these antibodies may inhibit the physiological function of FXII and contribute to the clinical symptoms suffered by this patient group. In our present study, we tested the antigenic binding site(s) of antibodies to FXII in patients with recurrent pregnancy losses. A difference between their study and our present study is that no patients studied fulfilled criteria for definite antiphospholipid syndrome in our study.

In conclusion, autoantibodies to FXII in patients with recurrent pregnancy losses recognize amino-terminal heavy chain region of FXII that is known as FXII-binding site to platelet glycoprotein Ibα. This suggests that autoantibodies to FXII in patients with recurrent pregnancy losses may inhibit the physiological role of FXII and thus contribute to the pregnancy loss.

Acknowledgements

Support from the Japan Society for the Promotion of Science to T. Sugi (818391813) is gratefully acknowledged.

References