INFLAMMATION AND INFLAMMATORY BOWEL DISEASE

Distribution and partial characterisation of IgG Fc binding protein in various mucin producing cells and body fluids


Background and aims: Mucins released from goblet cells is important in intestinal mucus defence, and mucin glycoproteins are thought to be major components of mucus. Recently, we identified and cloned another component of human colonic mucus, IgG Fc binding protein (FcγBP). FcγBP is immunologically distinct from known Fcγ receptors and its structure contains repeated cysteine rich unit sequences resembling those present in mucins. In this work, we assessed the tissue distribution of FcγBP, its binding activity in various body fluids, and its ability to inhibit complement mediated haemolysis.

Methods: Immunohistochemical localisation of FcγBP, using monoclonal antibodies against FcγBP (K9 or K17) and labelled IgG, was conducted in various mucin producing tissues: colon, small intestine, stomach, gall bladder, cystic duct, choledochus, bronchus, submandibular gland, conjunctiva, and cervix uteri. The binding activity of FcγBP in mucus extracted from colon, gastric juice, bile, nasal discharges, saliva, sputum, and tears was also examined by immunodot blot and immunoprecipitation using these monoclonal antibodies. Inhibition of complement mediated haemolysis by FcγBP was investigated using sheep red blood cells (SRBC) and anti-SRBC IgG.

Results: The immunohistochemical study revealed that mucin secreting cells in the colon, small intestine, gall bladder, cystic duct, choledochus, bronchus, submandibular gland, and cervix uteri contained FcγBP, and immunodot blot and immunoprecipitation analysis using IgG and monoclonal antibodies demonstrated that the fluids secreted by these cells were capable of binding IgG. Mucin producing cells of the conjunctiva did not express FcγBP molecules or bind to IgG. The surface mucous cells in the stomach were variably positive for FcγBP. Perhaps because of proteolytic degradation, FcγBP in gut lavage fluid did not have IgG binding activity, although this activity was present in the mucus covering the colon. FcγBP suppressed complement mediated haemolysis of SRBC.

Conclusions: FcγBP is widely expressed on mucosal surfaces and in external secretions. It is functionally intact in several fluids. These findings lend support to the concept that FcγBP is an important component of mucosal immunological defences.
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with Tris buffer solution (20 mM Tris HCl pH 7.4/0.15 M NaCl) containing 0.5% Tween 20 (TBS-T). Nitrocellulose paper was blocked with TBS-T containing 1% skimmed milk powder for 30 minutes to decrease non-specific binding and washed three times with TBS-T. Next, the paper was reacted with the mAbs K9, K17, a control IgG1 mAb (OE5) which was prepared in our laboratory against human asialoglycoprotein receptor, normal mouse IgG, or TBS-T for one hour at 37°C. After washing with TBS-T three times, the nitrocellulose paper was incubated with HRP-goat F(ab′)2 anti-mouse IgG for one hour at 37°C. Nitrocellulose paper was washed with TBS-T three times and developed with DAB solution. More than two samples of each fluid were examined.

**Immunoprecipitation for detection of FcγBP**

The supernatants prepared for immunodot blot were diluted twice with TBS-T containing 10 mM EDTA, 2 mM PMSF, and 0.005% soybean trypsin inhibitors. Each diluted supernatant was reacted with the mAbs K9, K17, OE5, or TBS-T for one hour at 37°C. After washing with TBS-T three times, the nitrocellulose paper was incubated with HRP-goat F(ab′)2 anti-mouse IgG for one hour at 37°C. Nitrocellulose paper was washed with TBS-T three times and developed with DAB solution. More than two samples of each fluid were examined.

**Figure 2**

Micrographs of serial cryostat sections of human stomach. Normal surface mucus cells (arrows) face the portion of intestinal metaplasia. (A) Normal surface mucus cells (arrows) and mucin producing cells in intestinal metaplasia (arrowheads) were stained by periodic acid-Schiff (arrowheads show the same portion on serial sections). (B) Normal surface mucus cells (arrows) were not stained by horseradish peroxidase-IgG whereas mucin producing cells of goblet cell-like intestinal metaplasia were stained. (C) Normal surface mucus cells (arrows) were weakly stained by the monoclonal antibody (mAb) K9. Mucin producing cells of intestinal metaplasia (arrowheads) were clearly stained by mAb K9 (200×).

**Figure 3**

Micrographs of mucin producing cells of various organs, immunohistochemically stained by horseradish peroxidase (HRP)-IgG and monoclonal antibodies (mAbs). Mucin producing cells of mucus glands in the choledochus (A) and bronchial glands (B) were stained with HRP-IgG. Mucin producing cells in the nasal glands (C), acinus of the submandibular gland (D), and cervical glands of the uterus (E) were stained by the mAb K9 (200×). Mucin producing cells stained by periodic acid-Schiff were all positive for HRP-IgG and mAbs.
HRP-goat F(ab')2 with mAb K17 after blocking with TBS-T containing 1% protein was transferred to nitrocellulose papers and incubated in each experiment. The protein was resolved in 8% sodium dodecyl sulphate-polyacrylamide gel electrophoresis. The positions of molecular weight standards were identified by rainbow marker (Bio-Rad Kaleidoscope Protein Standards) in each experiment. The protein was transferred to nitrocellulose papers and incubated with mAb K17 after blocking with TBS-T containing 1% skimmed milk powder. These papers were reacted with HRP-goat F(ab')2 antimouse IgG and developed with DAB solution. Nitrocellulose papers were washed three times with TBS-T between each incubation step.

**Inhibition of complement mediated haemolysis by FcγBP**

SRBC were washed three times with physiological saline containing 0.1% gelatine, 3 mM barbiturate, 1.8 mM barbital, 0.5 mM magnesium chloride, and 0.15 mM calcium chloride. Anti-SRBC rabbit IgG (100 µl; 300 µg/ml) was added to 1 ml of SRBC (1×10^8/ml) and incubated for one hour at 37°C. Next, 100 µl of the rich fraction of FcγBP (10K homogenate) (150 µg/ml) or PBS alone containing 10 mM EDTA, 2 mM PMSF, and 0.005% soybean trypsin inhibitors were added to this solution and incubated for one hour at 37°C. Then, 200 µl of rabbit complement (4 mg/ml), or PBS as a negative control, were reacted with this solution for one hour at 37°C. The reaction was stopped by chilling on ice. The solution was centrifuged at 1500 g for five minutes. The optical density of haemoglobin in supernatants was read at 541 nm. To further test the specificity of FcγBP in inhibiting haemolysis, two other control experiments were conducted. Firstly, an excess of non-immune rabbit IgG (600 µg/100 µl) was incubated with the 10K homogenate for one hour at 37°C. This solution was then added to SRBC bound anti-SRBC rabbit IgG and the complement was reacted. Secondly, to inactivate the function of FcγBP, the 10K homogenate was boiled for five minutes before being added to the haemolysis reaction mixture.

**RESULTS**

Localisation of FcγBP in tissues by immunohistochemistry and reaction with labelled IgG

As in our previous work, goblet cells in the normal colon and small intestine were stained by HRP-IgG and mAbs K9 and K17, but not by the irrelevant mAb OE5 (fig 1). In experiments to identify FcγBP positive cells in other tissues, mucin producing cells were detected by periodic acid-Schiff staining, and normal colon was used as a positive control for HRP-IgG binding and mAb staining. Surface mucus cells in the apparently normal stomach adjacent to intestinal metaplasia did not react with HRP-IgG, but these cells were weakly stained with the mAb in three of five samples. In contrast, mucin producing cells of goblet cell-like intestinal metaplasia of the stomach were positive for HRP-IgG binding as well as K9 and K17 staining (fig 2). Concerning the classification of intestinal metaplasia, two specimens showed the complete form of intestinal metaplasia and the third others the incomplete form. We found that both complete and incomplete forms of intestinal metaplasia were clearly positive for FcγBP and there was no difference in staining pattern between the two. We also examined three endoscopically biopsied samples of apparently normal stomach. All were negative for HRP-IgG binding and showed little or no staining (data not shown). All mucin producing cells of mucus glands in the choledochus, cistic duct, gall bladder near the cystic duct, and bronchial glands were not stained by the mAb K9 (200×). All intestinal metaplasia were clearly positive for HRP-IgG binding as well as K9 and K17 staining (fig 2). Concerning the classification of intestinal metaplasia, two specimens showed the complete form of intestinal metaplasia and the third others the incomplete form. We found that both complete and incomplete forms of intestinal metaplasia were clearly positive for FcγBP and there was no difference in staining pattern between the two. We also examined three endoscopically biopsied samples of apparently normal stomach. All were negative for HRP-IgG binding and showed little or no staining (data not shown). All mucin producing cells of mucus glands in the choledochus, cistic duct, gall bladder near the cystic duct, and bronchial glands were not stained by the mAb K9 (200×). All intestinal metaplasia were clearly positive for HRP-IgG binding as well as K9 and K17 staining (fig 2). Concerning the classification of intestinal metaplasia, two specimens showed the complete form of intestinal metaplasia and the third others the incomplete form. We found that both complete and incomplete forms of intestinal metaplasia were clearly positive for FcγBP and there was no difference in staining pattern between the two. We also examined three endoscopically biopsied samples of apparently normal stomach. All were negative for HRP-IgG binding and showed little or no staining (data not shown). All mucin producing cells of mucus glands in the choledochus, cistic duct, gall bladder near the cystic duct, and bronchial glands were not stained by the mAb K9 (200×).

**Table 1** Detection of IgG Fc binding protein by horseradish peroxidase [HRP]-IgG and monoclonal antibodies (mAbs) K9 and K17

<table>
<thead>
<tr>
<th>Tissue</th>
<th>HRP-IgG</th>
<th>K9</th>
<th>K17</th>
</tr>
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<tbody>
<tr>
<td>Colon (5/5)</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Small intestine (3/3)</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Stomach</td>
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<tr>
<td>Surface mucus cells</td>
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<td></td>
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<tr>
<td>Intestinal metaplasia</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Gall bladder (4/4)</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cystic duct (4/4)</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Choledochus (4/4)</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Bronchus (mucus gland)</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Nasal mucosa (mucus gland) (4/4)</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Submandibular gland (4/4)</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Conjunctiva (5/5)</td>
<td></td>
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<td></td>
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<tr>
<td>Cervix uteri (3/3)</td>
<td>+</td>
<td>+</td>
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*Surface mucus cells of the stomach showed negative stain with HRP-IgG, but in three of five samples these cells had a weak stain with the mAb and in two of five there was no stain.

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already demonstrated that human Fc by direct incubation with immunobeads (goat IgG). We have active control. Active Fc
In each experiment, the 10K homogenate was used as a posi-

IgG.

Immunoprecipitation and immunoblot for
characterisation of Fc

Immunoprecipitation with a mixture of the monoclonal antibodies (mAbs) and immunobeads. The molecules of FcyBP and active FcγBP were visualised on the paper. The 10K homogenate and mucus covering the colon had a 70–80 kDa band similar to that in lane 1. Gut lavage fluid had the 70–80 kDa band and a few smaller bands. The bands between 92 and 200 kDa are probably doublets and triplets of the 70–80 kDa band. Bands at about 50 kDa are heavy chains of the mAbs. From this result, it is evident that the 10K homogenate and mucus covering the colon contain active FcγBP but gut lavage fluid contains only fragments of FcγBP. Arrows show markers of 200 kDa (myosin), 92 kDa (phosphorylase), 64 kDa (bovine serum albumin), and 46 kDa (ovalbumin).

reduced conditions. The mAbs K9 and K17 were able to capture the molecules of FcγBP through the Fab region of the mAb besides the Fc region of the mAbs and goat IgG. In case of the 10K homogenate of the colon, immunoprecipitation with the mAbs identified the same 70–80 kDa band on the immunoblot as the active FcγBP with the immunobeads. Mucus covering the colon yielded the same results as those for the 10K homogenate. But no specific bands were found using normal mouse IgG. Gut lavage fluid did not show the 70–80 kDa band when it was immunoprecipitated only with immunobeads. However, the mAbs identified the 70–80 kDa band of FcγBP recognised by mAb K17 on the immunoblot (fig 7). Nasal discharges, sputum, and bile had almost the same IgG stained with HRP-IgG as well as with mAbs K9 and K17. In addition, all mucin producing cells in the nasal glands, acinus of the submandibular glands, and cervical glands of the uterus were also positive for HRP-IgG binding and mAb staining (fig 3) while mucin producing cells of conjunctivae were negative for reaction with these reagents (fig 4, table 1).

Immunodotblot for detection of FcγBP in secretions

Dots of the 10K homogenate and mucus covering the colon were stained by K9 and K17 but not by control OE5 or TBS-T (fig 5). In addition, normal mouse IgG showed no staining. Bile, nasal discharges, saliva, and sputum were positive for reaction with mAbs K9 and K17 but tears were negative (fig 6). Among five samples of gastric juice examined, two were positive but three were negative for reaction with both mAbs. The pH of the juices with positive staining was more than 6, whereas the pH of non-reactive juice was less than 3.

Immunoprecipitation and immunoblot for characterisation of FcγBP

In each experiment, the 10K homogenate was used as a posi-
tive control. Active FcγBP capable of binding IgG was detected by direct incubation with immunobeads (goat IgG). We have already demonstrated that human FcγBP can also bind to goat IgG. Immunoprecipitated active FcγBP was visualised at 70–80 kDa by immunoblot analysis with the mAb K17 under

Figure 5 Immunodotblot of the 10K homogenate or mucus covering the colon. The 10K homogenate or mucus covering the colon were dropped onto nitrocellulose paper and the paper was incubated with the monoclonal antibodies (mAbs) K9, K17, OE5 (irrelevant mAb), or TBS-T. Blots were then reacted with horseradish peroxidase-goat F(ab’2) antimouse IgG. K9 and K17 reacted positively but OE5 and TBS-T did not. 10K, 10K homogenate; M, mucus covering the colon.

Figure 6 Immunodotblot of various body fluids. Body fluids were dropped onto nitrocellulose paper and the paper was incubated with the monoclonal antibody (mAb) K17 and reacted with horseradish peroxidase-goat F(ab’2) antimouse IgG. Molecules of the IgG Fc binding protein (FcγBP) recognised by the mAb K17 were present in fluids, except gastric juice and tears. Incubation with TBS-T instead of mAb K17 showed no stain (C). 10K, 10K homogenate; M, mucus covering the colon; F, gut lavage fluid; G, gastric juice; B, bile; T, tears; N, nasal discharges; Sa, saliva; Sp, sputum.

Figure 7 Immunoprecipitation and immunoblot of the 10K homogenate [10K], mucus covering the colon (M), and gut lavage fluid (F). Lane 1: Immunoblot from direct immunoprecipitation with immunobeads (goat IgG antimouse IgG). The 70–80 kDa band is present on the nitrocellulose paper of the 10K homogenate and mucus covering the mucosa under reduced conditions but not on that of gut lavage fluid. Active IgG Fc binding protein (FcγBP) was captured by goat IgG via the Fc portion. Lane 2: Immunoblot from immunoprecipitation with a mixture of the monoclonal antibodies (mAbs) and immunobeads. The molecules of FcγBP and active FcγBP were visualised on the paper. The 10K homogenate and mucus covering the colon had a 70–80 kDa band similar to that in lane 1. Gut lavage fluid had the 70–80 kDa band and a few smaller bands. The bands between 92 and 200 kDa are probably doublets and triplets of the 70–80 kDa band. Bands at about 50 kDa are heavy chains of the mAbs. From this result, it is evident that the 10K homogenate and mucus covering the colon contain active FcγBP but gut lavage fluid contains only fragments of FcγBP.
believed to have a major role.

Among a number of the components of mucus, mucins are widely distributed in mucus cells and secreted mucins. Nasal discharges had the 70–80 kDa band similar to that of the 10K homogenate in both lanes 1 and 2. Sputum and bile showed the same faint band as the 10K homogenate. Thus these fluids contain active FcγBP.

**Inhibition of complement mediated haemolysis by FcγBP (fig 9)**

SRBC reacted with anti-SRBC rabbit IgG were haemolysed after incubation with complement. Addition of the 10K homogenate containing FcγBP significantly (p<0.01) inhibited complement mediated haemolysis. Addition of excess non-immune rabbit IgG (to bind the FcγBP) to the 10K homogenate before incubation with complement abolished the inhibitory effect of FcγBP. Addition of heat treated (inactivated) FcγBP to the reaction had no inhibitory effect on haemolysis. From these results, we conclude that the rich fraction of FcγBP specifically inhibited complement mediated haemolysis of SRBC.

**DISCUSSION**

Intestinal mucus is probably critical in protecting the gut against harmful antigens and in providing a physiological barrier against the harsh luminal environment.1,2 However, the protective mechanisms involved are poorly defined. Among a number of the components of mucus, mucins are believed to have a major role. The high molecular weight mucins are responsible for the viscoelastic properties of the mucus barrier. They are widely expressed in epithelial tissues and are characterised by variable number tandem repeat peptide sequences rich in serine, threonine, and proline which carry large numbers of O linked oligosaccharide chains. To date, 13 mucins have been identified and their functions and activities of FcγBP and to begin characterising the activities of FcγBP. Our major findings were that FcγBP was widely distributed in mucus cells and secreted mucins. Furthermore, it retained IgG binding activity in several fluids and could inhibit a complement mediated reaction of IgG.

For use in the present study, we chose two mAbs (K9 and K17) to human FcγBP from among 14 mAbs we had previously made. We had shown previously that both mAbs K9 and K17 strongly stained goblet cells in the human colon and inhibited in vitro binding of HRP-IgG to cells in tissue sections. The mAb K9 showed the highest titres in three types of ELISA to detect FcγBP and stained goblet cells under various conditions of fixation, including 10% formalin, 0.5% glutaraldehyde, and 100% ethanol. Only mAb K17, among the mAbs which block binding of HRP-IgG in tissue sections, detected the 70–80 kDa band in immunoblot studies under reduced conditions. The material reactive with mAb K9 did not cross react with the propolypeptide of von Willebrand factor by amino acid sequence homology7 but the material reactive with mAb K17 did cross react with it. These antibodies did not react with MUC2, Muc5AC, MUC5B, or MUC6.

In the present study, we examined the existence and activity of FcγBP in various external body fluids and immunohistochemically identified the binding protein in various tissues. Initially, we found that gut lavage fluid did not have IgG binding activity when applied to a column of Sepharose linked to IgG. To determine whether various body fluids contain active FcγBP or only fragments of FcγBP a mixture of the fluids and mAbs were incubated with immunobeads (goat IgG anti-mouse IgG), and the captured molecules were detected by mAb K17. Normal mouse IgG was unable to bind human...
FcγBP through its Fc portion, unlike human or goat IgG, as found in previous experiments. As the Fc portion of mouse IgG has at least 128 times less affinity to human FcγBP than the Fab portion of the mAb against FcγBP9, non-specific binding of mouse IgG to FcγBP was negligible and fragments of FcγBP were detected by the mAb as efficiently as was active FcγBP.

In the stomach, we found that although some surface mucous cells were slightly stained with K9 and K17. HRP-IgG did not bind to cells. We suspect that this failure of immunoreactive FcγBP to bind HRP-IgG reflects degradation or damage of the FcγBP binding sites(s) by the acidic gastric environment. FcγBP was detected by the immunodot blot assay in gastric juice with a pH of 6 or more. Thus FcγBP may be secreted by the normal stomach but we cannot be certain that FcγBP detected by the immunodot blot in presumably normal gastric juice had not been secreted by gastric intestinal metaplasia cells or was present in duodenal juice or bile that had refluxed into the stomach. Recently, 13 types of mucins have been reported and the normal stomach is characterised by expression of MUC1, MUC5AC, and MUC6.13-16 Expression of mucin is different in different types of intestinal metaplasia, and Helicobacter pylori infection alters expression of mucin.17-21 Although we did not examine our patients for H. pylori, all five specimens from patients with gastric cancer had intestinal metaplasia and the distribution of FcγBP was almost negative in apparently normal gastric mucosa adjacent to intestinal metaplasia. In addition, surface mucous cells in the apparently normal stomach adjacent to intestinal metaplasia did not react with HRP-IgG but these cells were weakly stained with mAbs in three of five samples. Thus variations in the environment of the stomachs of our patients may explain the variability in the results of FcγBP in the gastric samples. Further investigations on the expression and distribution of FcγBP in relation to H pylori infection and the types of intestinal metaplasia are warranted to clarify the role of FcγBP in the stomach.

Mucus cells of the conjunctiva did not bind to HRP-IgG, and FcγBP was not detected in tears, even though some mucins (MUC1, MUC4, and MUC5AC)23 and mucin associated trefoil peptides (pS2 and intestinal trefoil factor)13 are present on the ocular surface, while the ocular surface does not express less mucins than the gastric epithelium (MUC1, MUC6, and MUC5AC) or the colonic surface (MUC1, MUC2, MUC3, and MUC4).24-26 Although the reason why FcγBP is not expressed on the ocular surface is unknown, it may be that the conjunctiva or cornea comes from an embryologically different origin (ectoderm) from that of the epithelium of the digestive or respiratory tracts (endoderm).

FcγBP was originally identified in intestinal goblet cells and demonstrated to be secreted with mucus into the intestinal lumen.27 In fact, we found IgG activity and molecules detected by mAbs abundant in the mucus obtained from the surface of the large intestine, whereas IgG binding activity was not detected in the lavage fluid collected at endoscopy of the large intestine. However, immunoprecipitation detected the degraded smaller molecules in addition to the 70–80 kDa molecule. These findings may indicate that FcγBP released into the intestinal lumen is degraded by digestive enzymes resulting in inhibition of IgG binding activity. In contrast, FcγBP is not degraded in nasal discharges, sputum, or bile. FcγBP strongly binds aggregated IgG and IgG complexes. Thus we have speculated that FcγBP helps to protect the gut mucosal surface by binding IgG molecules in complexes with antigens, including infectious microorganisms. This activity may facilitate clearance of the complexes from mucosal surfaces. If this were the case, degradation of FcγBP in gut secretions may seem to be counterproductive. However, it is possible that FcγBP is not degraded once complexed with IgG.

Another important finding of this work was that FcγBP inhibited complement mediated haemolysis of SRBC. Complement mediated reactions involving IgG molecules on mucosal surfaces or in external secretions may be injurious. Thus a mechanism for inhibiting such reactions might be beneficial. Normally, not much IgG is present in external secretions. However, as in inflammatory diseases, FcγBP may prevent injurious complement mediated reactions from occurring by binding any available IgG. Interestingly in this regard, we found increased amount of FcγBP antigen in the sera of patients with inflammatory bowel diseases and autoimmune diseases. Taken together, we suggest that FcγBP plays a role in the protection of tissue damage by immune complexes in the intestinal wall.

In summary, our findings that FcγBP is present widely throughout mucous membranes and in external body fluids, that FcγBP retains IgG binding activity in many fluids, and that FcγBP can inhibit a complement mediated reaction, suggest that this novel mucin is important in the immunological defence of mucosal surfaces. Further study of the biological importance of FcγBP is warranted.

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Distribution and partial characterisation of IgG Fc binding protein in various mucin producing cells and body fluids

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