Pemphigus foliaceus (PF) is a human autoimmune disease in which antibodies (IgG) are directed against the cell surface of epidermal cells with resultant blister formation (1). Patients with PF develop small blisters that quickly evolve into scaly and crusted skin lesions, often in a seborrheic distribution. Mucous membranes are usually not involved. The histopathology of the blisters demonstrates that cells in the superficial epidermis have detached from each other, a pathologic process called acantholysis (1, 2). Electron microscopic studies of early lesions of PF show diminished numbers (to complete loss) of desmosomes and abnormalities of the tonofilament-desmosome complex (2). Direct immunofluorescence demonstrates that IgG is bound to the cell surface of epidermal cells, and most patients also have circulating antibodies that bind to the surface of cells in normal epidermis as detected by indirect immunofluorescence.

PF is clinically and histologically distinct from pemphigus vulgaris (PV), the other major form of pemphigus (1). Patients with PV typically have erosions of mucous membranes and often display erosions over large areas of the skin. Histology of the blister in PV demonstrates acantholysis deep in the epidermis, as opposed to the superficial blister seen in PF. The ultrastructural descriptions of the blisters in PF and PV also differ. In contrast to the desmosomal abnormalities described in early blisters of PF, electron microscopy of blisters in PV demonstrates initial loss of cell cohesion between intact desmosomes (3).

Patients with PV, like those with PF, usually have both in vivo-bound and circulating antibodies to the cell surface of epidermal cells (1, 4). However, we have recently shown (5) that the molecular specificities of PV and PF antibodies are distinct. Autoantibodies from different PV patients bind the same molecule, a glycoprotein with disulfide-linked chains of 130,000 and 80,000 mol wt, synthesized by epidermal cells in culture (5, 6). PF antibodies, in general, do not bind this molecule. On the other hand, circulating antibodies from about half of...
PF patients, but not from PV patients, react strongly with a 160,000 mol wt polypeptide extracted from normal human epidermis and identified as a broad band by sodium dodecyl sulfate (SDS) polyacrylamide gel electrophoresis (PAGE).2

Desmoglein (DG) I (also called desmosome group 3 protein) is a desmosomal core glycoprotein with a molecular weight similar to that of PF antigen (7–12). By SDS-PAGE analysis, DGI isolated from bovine muzzle desmosomes appears as a broad band at ~150,000–175,000 mol wt (7–12). On gradient gels, this band can sometimes be resolved into a triplet of three closely spaced bands that are immunologically and chemically related (9). DGI is considered a core protein of the desmosome because it is enriched in desmosome core preparations (7) and, in addition, preliminary immunoelectron microscopic studies have localized DGI to the intercellular space (core) of the desmosome (13). Immunofluorescence studies with antibodies to DGI that were isolated from bovine muzzle desmosomes have demonstrated DGI in human epidermis (11).

Since DGI and PF antigen are of similar molecular weight, and because PF is a disease of cell adhesion with desmosomal abnormalities, we sought to determine in this study if the PF antibodies that bind the 160,000 mol wt protein extracted from normal human skin are directed against DGI. We demonstrate that auto-antibodies from these PF patients, but not from PV patients, are directed against this desmosomal core glycoprotein.

Materials and Methods

Human Epidermal and Desmosomal Extracts. Normal human epidermis, obtained by excising the roofs of suction blisters induced on the volar forearm of volunteers, was extracted with sample buffer (2% SDS, 0.0625 M Tris-HCl, pH 6.8) (14). Desmosomes were isolated from bovine muzzle using nonionic detergent in citrate buffer and differential centrifugation, as previously described (7). The desmosomal pellet was extracted with sample buffer in preparation for SDS-PAGE.

One-Dimensional and Two-Dimensional Gel Electrophoresis. One-dimensional SDS-PAGE, under reducing conditions, was performed on 5 or 6% acrylamide slab gels as described by Laemmli (15). Two-dimensional gel electrophoresis was essentially performed as described by O'Farrell (16), modified by Ames and Nikaido (17) for proteins extracted with SDS. In brief, the epidermal extract in sample buffer was diluted with 2 vol of 9.5 M urea, 2% ampholines (LKB Produkter, Bromma, Sweden), pH 3.5–9.5, 10 mM dithiothreitol, and 8% Nonidet P-40. Isoelectric focusing was then performed in 4% acrylamide tube gels at 300 V overnight, then at 600 V for 1 h. The tubes were then equilibrated with 0.1 M dithiothreitol, 0.01% bromophenol blue, and 10% glycerol in sample buffer, and placed horizontally on top of a 4% acrylamide stacking gel on a 5% acrylamide running gel for SDS-PAGE. The proteins thus resolved in two dimensions were then used for immunoblotting.

Immunoblotting. To identify PF antigen and DGI, we used a previously described immunoblotting procedure (5, 14). In brief, proteins that were extracted either from normal human epidermis or from bovine muzzle desmosomes were separated by one- or two-dimensional electrophoresis, then electrophoretically transferred to either nitrocellulose sheets or 2-aminophenylthioether (APT) paper, which binds proteins covalently. Proteins were then identified using immunoperoxidase staining with specific antibodies. Sera, which have been previously described, from patients with histologically confirmed PF, were used to identify PF antigen (5). By indirect immunofluorescence on normal human skin or monkey esophagus, these sera stained in a cell surface pattern throughout

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2 This molecule, defined by this subgroup of PF patients, will be referred to as PF antigen.
the epithelium with a titer of >40. As controls, sera from patients with PV, with equivalent immunofluorescent titers as previously reported (5), and normal human sera were used. A rabbit antiserum raised to isolated bovine muzzle desmosomes (7) was used to identify various desmosomal proteins. DGI, isolated from bovine muzzle desmosomal cores by SDS-PAGE, was used to raise a rabbit antiserum. This antiserum, called RpDGI-1, specifically stains DGI and not other desmosomal proteins (12).

Affinity Purification of Antibodies Binding PF Antigen. Affinity purification was accomplished as previously described (5). In short, PF serum was incubated with epidermal extracts that were separated by SDS-PAGE and transferred to APT paper. The antibodies which bound the 160,000 mol wt PF antigen were eluted using 0.5 M NaCl, 0.5 M acetic acid, pH 2.5, and then neutralized and concentrated. These affinity-purified antibodies were used for immunoblotting to stain DGI.

Results

Antibodies from Certain PF Patients Specifically Bind a 160,000 Mol Wt Protein. Proteins in extracts of normal human epidermis were separated by SDS-PAGE, then electrophoretically transferred to nitrocellulose or APT paper. Lanes of separated protein were cut out and stained by the use of an immunoperoxidase technique. Fig. 1 demonstrates that, consistent with our previous findings (5), sera from three of four PF patients demonstrate a strong reaction with a 160,000 mol wt polypeptide that appears as a broad band. PV sera and normal human sera do not stain this band. To date, we have tested 13 PF sera, 9 PV sera, 9 normal human sera, and sera from 9 patients with bullous pemphigoid, which is another autoimmune blistering disease of the epidermis. Consistent and heavy staining of this 160,000 mol wt band was obtained with 6 of the 13 PF sera, but with none of the other sera, used as controls. These data indicate that circulating antibodies to this specific polypeptide, that is extracted from normal human epidermis, are characteristic of a subgroup of PF patients. We will refer to this molecule as PF antigen.

![Figure 1](image.png)

**Figure 1.** Certain PF sera specifically bind an ~160,000 mol wt polypeptide (PF antigen) extracted from normal human epidermis. Proteins in extracts of normal human epidermis were separated by SDS-PAGE (5% acrylamide). A Coomassie Blue stain of the separated proteins is shown in the lane marked CB. Identical lanes of proteins were electrophoretically transferred to APT paper and then immunoperoxidase staining was performed with PF sera. (Different numbers indicate sera from different patients). Sera from patients with PV (another autoimmune blistering disease of the skin which is clinically, histologically, and immunochemically distinct from PF) and normal human sera (N) were used as specificity controls. Molecular weight standards (myosin, phosphorylase B, albumin) that were run concurrently (not shown) were used to calculate the apparent molecular weight of the stained band. Three of the four PF sera shown specifically stained a broad polypeptide band at ~160,000 mol wt (arrow).
Antibodies against DGI Bind the PF Antigen Extracted from Normal Human Epidermis. Fig. 2 shows immunoblot analysis of proteins, from extracts of normal human epidermis, separated by SDS-PAGE. Rabbit antibodies raised against isolated bovine muzzle desmosomes identify polypeptides with molecular weights similar to the bovine muzzle desmoplakins (DP), proteins found in the desmosome plaque (8, 10, 18), and desmogleins (DG), glycoproteins that are enriched in desmosomal core preparations (7, 9, 12). (Fig. 2, lane 1). PF antibodies identify PF antigen (Fig. 2, lane 3), which co-migrates with DGI. The antibody RpDGI-1, raised in rabbits to DGI from bovine muzzle desmosomes, identifies the DGI in these immunoblots (Fig. 2, lane 5). PF antigen (Fig. 2, lanes 7, 8), identified by PF sera, co-migrates with DGI. The apparent molecular weight of these molecules from human epidermis is 160,000, slightly higher than the 150,000 mol wt reported for DGI from bovine muzzle desmosomes; however, slight differences in molecular weight of desmosomal proteins in different tissues have been previously reported (10, 12). The specificity of the binding of both PF antibodies and RpDGI-1 is demonstrated by the findings that: (a) they both stain only one minor protein band of the many bands (Fig. 2, lane 11) that were transferred to the APT paper, and (b) normal human sera (Fig. 2, lanes 4, 9, 10) and normal rabbit sera, (Fig. 2, lanes 2, 6), used as controls, do not stain this band.

Additional evidence that PF antibodies and antibodies to DGI bind the same
protein was provided by two-dimensional gel electrophoresis. Proteins in extracts of normal human epidermis were separated by isoelectric focusing in the first dimension and by SDS-PAGE in the second dimension. The proteins thus separated were transferred to nitrocellulose sheets for immunoperoxidase staining. Fig. 3 demonstrates that PF antibodies and antibodies to DGI stain the same spots at apparent molecular weight 160,000 and pH 5.4–5.7. Normal human serum and normal rabbit serum, used as controls, do not stain these spots. Taken together, these data indicate that rabbit antibodies to the bovine muzzle desmosomal glycoprotein DGI recognize the PF antigen extracted from normal human epidermis.

**PF Antibodies Bind DGI Extracted from Bovine Muzzle Desmosomes.** Extracts of isolated bovine muzzle desmosomes, electrophoresed by SDS-PAGE, demonstrate multiple polypeptide bands including DPI, DPII, DGI, DGII, and DPIII (7-10, 12, 18) (Fig. 4, lane 1). Of these polypeptides, PF serum specifically stained DGI (Fig. 4, lane 2). PV serum and normal human serum, used as controls, did not stain any of these polypeptide bands (Fig. 4, lanes 3 and 4). Three of the four PF sera tested in similar experiments specifically stained DGI. The failure of one PF serum to stain the DGI from bovine muzzle desmosomes may be due to species specificity of this antibody.

In additional experiments, PF antibodies were affinity purified using PF antigen extracted from normal human epidermis and bound to APT paper, which binds proteins covalently. These antibodies, eluted from the PF antigen 160,000 mol wt band and used for indirect immunofluorescence, stain sections of normal human skin in an epidermal cell surface pattern identical to that seen

Figure 3. Co-migration of PF antigen and DGI on immunoblots of extracts of normal human epidermis electrophoresed in two dimensions. Isoelectric focusing (IEF) was performed in the first (horizontal) dimension (acid end on left) and SDS-PAGE in the second (vertical) dimension. (a) Immunoperoxidase staining with RbDGI-1, rabbit anti-DGI, indicates two major spots (~160,000 mol wt, pH 5.4–5.7). (b) Control normal rabbit serum used for immunoperoxidase staining did not stain these spots. (c) PF serum (No. 457) stained major spots that co-migrate with DGI shown in a. (d) Control normal human serum did not stain these spots.
PF autoantibodies bind DGI extracted from bovine muzzle desmosomes. The results of SDS-PAGE immunoblot analysis of extracts of isolated bovine muzzle desmosomes are shown. (Lane 1) Amido black staining demonstrates the previously described desmosomal proteins DGI (arrow), and (arrowheads, from top to bottom) DPI, DPII, DGIIa, DGIIb, DPIII (7-12). (Lane 2) Arrow demonstrates immunoperoxidase staining of 150,000 mol wt broad band of DGI by PF serum (No. 175). (Lane 3) PV serum does not specifically stain any bands from the desmosomal extract. (Lane 4) Normal human serum also does not specifically stain any bands.

Immunoperoxidase staining of DGI from bovine muzzle desmosomes by affinity-purified PF IgG. Isolated bovine muzzle desmosomes were subjected to SDS-PAGE in two identical lanes. These lanes were electrophoretically transferred to nitrocellulose strips. One lane (lane 1) was stained with amido black to determine the position of the proteins. Using lane 1 as a guide, we cut out 4-mm-diam circles from unstained lane 2 at the location of the 150,000 mol wt band (DGI) and the 240,000 mol wt band (DPI). Immunoperoxidase staining of lane 2 was then performed with a rabbit antibody raised to desmosomes isolated from bovine muzzle. The staining, shown here, demonstrates that the circles were indeed cut out from the 150,000 mol wt and the 240,000 mol wt bands. The circles (shown under 1) were subjected to immunoperoxidase staining with PF IgG that was affinity purified on PF antigen extracted from normal human epidermis. The affinity-purified PF IgG stained the 150,000 mol wt (DGI) circle, but not the 240,000 mol wt (DPI) circle, which was used as a control.

These affinity-purified PF antibodies also specifically bound DGI extracted from isolated bovine muzzle desmosomes (Fig. 5).

Discussion

This report demonstrates that both antibodies to the desmosomal core protein DGI isolated from bovine muzzle desmosomes and autoantibodies from certain
PF patients bind to the same ~160,000 mol wt polypeptide extracted from normal human epidermis. Moreover, these PF antibodies also bound to DGI extracted from bovine muzzle desmosomes. Taken together, these data indicate that autoantibodies to a desmosomal core protein, DGI, are found in some patients with PF, a disease characterized by loss of adhesion of epidermal cells. It is tempting to speculate that these autoantibodies might directly contribute to this acantholysis. However, if these antibodies do cause loss of cell adhesion, why are lesions only seen in the superficial epidermis and not in other areas of the epidermis, and not in other epithelial tissues that also contain desmosomes? Several possible explanations exist: (a) There are probably many molecules important in cell-to-cell adhesion. If DGI is, in fact, one of them, its relative contribution to cell adhesion may be greater in the superficial epidermis than in other tissue locations. (b) Although related proteins, including DGI, are seen in desmosomes from different epithelial tissues, there are tissue-specific chemical differences among them (10, 12). In addition, subtle differences, related to the degree of keratinization, may exist between desmosomes at different levels of the epidermis (2, 19, 20). Thus, antibodies may interact differently with desmosomes in different locations. (c) Antibodies may not directly interfere with cell adhesion, but may act through other mechanisms which themselves might be tissue specific. For example, in PV, which is also an autoimmune disease of epidermal cell adhesion, autoantibodies that bind to the epidermal cell surface trigger the release of one or more proteolytic enzymes which subsequently result in acantholysis (21–26). This mechanism has also been shown to be operative in some cases of PF (25). Whether this mechanism holds for the subgroup of PF patients with autoantibodies to DGI is not known.

In evaluating previous reports (1, 5, 6) that address the question of pemphigus antibody reactivity with desmosomes, it is crucial to consider that PV and PF are clinically, histologically, and immunochemically distinct diseases. Furthermore, even sera from different PF patients may demonstrate antigenic heterogeneity, as shown in the present and a previous report (5). These considerations may account for the seemingly contradictory findings, regarding pemphigus antibodies and desmosomes, of different studies. For example, Jones et al. (28), using antidesmosomal and pemphigus antibodies in an immunofluorescence assay, recently reported that pemphigus sera bind to desmosomes of mouse epidermal cells in culture. These findings may be consistent with the present report, but it would be important to know the type of pemphigus sera used. On the other hand, Gorbsky et al. (29), using an enzyme-linked immunoassay of bovine desmosomal proteins and immunofluorescence of monkey esophagus, concluded that PV antibodies do not bind to desmosomal proteins. This conclusion is also consistent with the findings of the present study that only certain PF, but no PV, antibodies bind to a desmosomal glycoprotein.

The precise relationship of the antidesmosomal antibodies in some PF patients to the pathophysiology of the disease remains to be determined. Antibodies to desmosomes may not be related to the pathogenesis of the disease, but may instead be secondary to autoimmunization once the disease is active. This explanation seems unlikely because both PV and PF antibodies are capable of causing blister formation (25, 30).
is not known, the present study suggests that autoantibodies found in some PF patients may interfere with cell adhesion mediated by a desmosomal core protein. Additional study of this human autoimmune disease should further our understanding of the function of this desmosomal molecule.

Summary

Pemphigus foliaceus (PF) is a human autoimmune disease in which antibodies are directed against the cell surface of epidermal cells with resultant blister formation. The histopathology of these blisters indicates that cells have detached from each other, and electron microscopy of early blisters shows diminished numbers, to complete loss, of desmosomes as well as abnormalities of the tonofilament-desmosome complex. In this study we demonstrate that autoantibodies from certain PF patients bind to a desmosomal core glycoprotein called desmoglein (DG) I. Proteins in extracts of normal human epidermis were separated by sodium dodecyl sulfate (SDS) polyacrylamide gel electrophoresis (PAGE), then transferred to nitrocellulose or 2-aminophenylthioether paper for immunoperoxidase staining. Results of these immunoblots indicated that sera from 6 of 13 PF patients specifically and intensely stained an ~160,000 mol wt polypeptide, "PF antigen". Such staining was not seen with normal human sera or sera from patients with pemphigus vulgaris or bullous pemphigoid, two autoimmune blistering skin diseases that are clinically, histologically, and immunochemically distinct from PF. However, rabbit antiserum directed against DG I, that was isolated from bovine muzzle desmosomes, stained a polypeptide band which co-migrated with PF antigen. Furthermore, when proteins from extracts of normal human epidermis were electrophoresed in two dimensions (isoelectric focusing, then SDS-PAGE) before transfer to nitrocellulose for immunoperoxidase staining, PF antibodies and antibodies to DG I stained identical spots. Finally, PF sera as well as PF IgG that was affinity purified with PF antigen from normal human epidermis, both selectively bound to DG I extracted from bovine muzzle desmosomes. These studies demonstrate that the human autoantibodies from certain patients with PF, a disease of epidermal cell adhesion, are directed against a desmosomal core protein.

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