Desmoglein as a target in skin disease and beyond

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Abstract

Much of the original research on desmosomes and their biochemical components was through analysis of skin and mucous membranes. The identification of desmogleins 1 and 3, desmosomal adhesion glycoproteins, as targets in pemphigus, a fatal autoimmune blistering disease of the skin and mucous membranes, provided the first link between desmosomes, desmogleins, and human diseases. The clinical and histological similarities of staphylococcal scalded skin syndrome or bullous impetigo and pemphigus foliaceus led us to identify desmoglein 1 as the proteolytic target of staphylococcal exfoliative toxins. Genetic analysis of striate palmoplantar keratoderma and hypotrichosis identified their responsible genes as desmogleins 1 and 4, respectively. More recently these fundamental findings in cutaneous biology were extended beyond the skin. Desmoglein 2, which is expressed earliest among the four isoforms of desmoglein in development and found in all desmosome-bearing epithelial cells, was found to be mutated in arrhythmogenic right ventricular cardiomyopathy and has also been identified as a receptor for a subset of adenoviruses that cause respiratory and urinary tract infections. The story of desmoglein research illuminates how dermatologic research originally focused on one skin disease, pemphigus, has contributed to understanding biology and pathophysiology of many seemingly unrelated tissues and diseases.

Keywords
pemphigus; impetigo; hypotrichosis; cardiomyopathy; cadherin

Introduction

The story of the discovery of desmogleins in desmosomes, their relationship to adhesion molecules, and their targeting in diseases with loss of adhesion of cells is one of beautiful simplicity and logic, in which the research in skin has played a major role. This review will tell that story (Table 1).

The story starts with the discovery of desmosomes by electron microscopy and observations that they play a role in adhesion of keratinocytes. Dermatologists already know intuitively
that desmosomes are important in cell adhesion, because in spongiosis, one of the most common pathologies seen in inflammatory skin diseases such as allergic contact dermatitis, there is edema between keratinocytes separating their cell membranes, yet the cells stay attached right at the desmosomes (also called in the past “intercellular bridges”). Only when the desmosomes finally “dissolve” does a spongiotic blister form. It was in skin and stratified squamous epithelial tissue in which the presence and importance of desmosomes was discovered, but subsequently they were discovered in non-epithelial tissues such as heart (see below).

Biochemical and molecular characterization of desmogleins

Once a method of isolating desmosomes from epithelia (cow’s snout was the major source) was established, they could be biochemically characterized. The central part of the desmosome, as seen by electron microscopy as a white area between the cell membranes of adjacent cells, was thought to be the “glue” that held the desmosomes (and, thereby, the cells) together. When this area was enriched from the isolated desmosomes, its protein composition could be determined. A major protein was identified of about 160 kd, and was called desmoglein, “glein” derived from the Greek word for “glue”.

Subsequently antibodies against desmoglein were developed. These antibodies indicated that desmoglein was found in desmosomes of various tissues across various species. Desmoglein, therefore, was determined to be a widespread, and presumably important (i.e. conserved through evolution), component of the desmosome. From this work, initially in epidermis, it was found that desmoglein was also found in many other tissues such as intestine, mammary gland, trachea, bladder, liver, and, perhaps unexpectedly, heart and thymus.

Protein isolation and antibodies allowed molecular cloning of desmoglein. Surprisingly, desmoglein was found to be a group of homologous molecules encoded by a gene family. The most interesting, and scientifically satisfying, finding was that desmogleins were in a supergene family defined by classical cadherins, which were already known to be calcium-dependent adhesion proteins. Thus, desmogleins, thought the be part of the “glue” in desmosomes, were found to be in a family of adhesion molecules; a very nice convergence of deductions from early morphologic findings and newer genetic cloning techniques.

The first two members of the desmoglein gene family were identified by genetic cloning as desmoglein 1 and 2, but a dermatologic disease, pemphigus vulgaris, allowed identification of a third member (see below), desmoglein 3. Analysis of the human genome database identified another desmoglein, desmoglein 4, which was also identified by mutational analysis of a genetic hair disease (localized autosomal recessive hypotrichosis) (Table 1).

Even at this early stage, characterization of a desmoglein gene family was closely intertwined with understanding skin diseases. However that interdependency reached another level when the relationship of pemphigus to desmogleins was defined.
Desmogleins identified as targets of autoantibodies in pemphigus

There are two major types of pemphigus, vulgaris and foliaceus. In both, blisters are caused from loss of cell adhesion in the deep epidermis or superficial epidermis, respectively. Pemphigus vulgaris affects mucous membranes and/or skin, whereas pemphigus foliaceus only affects skin. In both, autoantibodies are known to directly mediate the loss of cell adhesion.

The original discovery that these diseases are related to desmosomes depended on a precious commodity, time, that today (with increasing demands related to extensive grant writing; extensive regulation; the geometric progression of required educational modules for; routine clinical, laboratory and animal work; demands to earn their salaries by seeing patients; and more) is much less available. But the availability of time was the critical resource that allowed one of the authors (JRS), in early 1980, to attend a lecture by Malcolm Steinberg at Dulles Airport, 40 minutes from where I worked in Bethesda. At that time, I had been working on identifying the autoantigen in pemphigus foliaceus and knew it was an approximately 160 kd protein as identified by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) of epidermal extracts, followed by immunoblotting. This was precisely the same time that Malcolm Steinberg (with G. Gorbsky) was dissecting the proteins in the “desmoglea” (the electron lucent center) of the desmosome. There was no evidence then that pemphigus had anything to do with desmosomes, but since cells come apart in pemphigus I was interested in cell adhesion and, therefore, desmosomes. Since I had enough time to take several hours to attend that talk, I learned that Dr. Steinberg had identified the first desmoglein, now called desmoglein 1, as a 160 kd glycoprotein. Naively, I thought that it would make sense if desmoglein 1 was the pemphigus foliaceus antigen, because both were the same size as determined by SDS-PAGE. (Ignorance is also sometimes a great advantage to a scientist; I had no idea how many molecules extracted from epidermis might migrate in the same general area on a one dimensional SDS-PAGE gel).

In fact, the pemphigus foliaceus antigen was ultimately shown to be desmoglein 1 (Figure 1), and desmoglein 1 was shown to be in the superficial epidermis. This finding showed the first autoimmune disease of desmosomes, and had the scientifically satisfying logic that an antibody against a presumed cell adhesion molecule in a cell adhesion structure causes a disease from loss of cell adhesion and subsequent blister formation.

At the time the pemphigus foliaceus antigen was shown to be desmoglein 1, the pemphigus vulgaris antigen was only known to be a glycoprotein of about 130 kd, as determined by immunoprecipitation. In addition, it was known there was some relationship of the pemphigus vulgaris antigen to desmosomes because it was shown by co-immunoprecipitation that pemphigus vulgaris antigen co-precipitated plakoglobin with the 130 kd molecule. Similarly pemphigus foliaceus sera co-precipitated plakoglobin with desmoglein 1. Plakoglobin was known to be in the plaque of the desmosome inside the cell. These studies were the first to show that the tail of desmogleins (the part inside the cell) bound a plaque protein of the desmosome. Again, a skin disease, pemphigus, was
intertwined with our growing understanding of desmosomes, in this case their molecular structure.

What really brought all these observations together, in a beautiful and logical synthesis of previous findings, was the molecular cloning of pemphigus vulgaris antigen which showed it was another, previously unknown, desmoglein, now called desmoglein 3 (Figure 2). Although desmoglein 1 and 3 were both found in epidermis, they were at different levels; desmoglein 1 was superficial and desmoglein 3 was deep. All the previous observations and findings now fit together nicely: Pemphigus vulgaris and foliaceus were closely related diseases that both had loss of keratinocyte adhesion but in different tissue localizations. The autoantibodies bound closely related molecules thought to provide the “glue” in adhesion structures, the desmosomes, with resultant loss of adhesion and blisters. In pemphigus vulgaris and foliaceus the blisters were thought to occur in different tissue localizations because of the different localizations of the desmogleins. Finally, both pemphigus antigens were found to bind plakoglobin because desmogleins bind plakoglobin by their homologous tails.

Many more subsequent studies confirmed that the anti-desmoglein antibodies in pemphigus patients cause the disease. For example, adsorption of pemphigus sera with recombinant desmogleins resulted in loss of pathogenicity of those sera. Monoclonal anti-desmoglein antibodies cause disease when injected into neonatal mice or human skin organ culture (Figure 3). An interesting confirmation that loss of desmoglein 3 adhesion causes pemphigus is that mouse with a genetic deletion of desmoglein 3 develop oral and skin lesions with the typical histology of pemphigus vulgaris. Finally, specific proteolytic cleavage of desmoglein 1 caused lesions in epidermis histologically indistinguishable from pemphigus foliaceus (see below).

**Desmogleins used for the diagnosis of pemphigus**

cDNA isolation of desmoglein 1 and 3 allowed us to produce recombinant proteins which properly reflect their three dimensional structures by baculovirus or mammalian expression. The immunoadsorption of patients’ sera with those recombinant proteins removed their immunoreactivities on keratinocyte cell surfaces by immunofluorescence and their ability to induce blister formation in neonatal mice. Subsequently, enzyme-linked immunosorbent assay (ELISA) using recombinant desmogleins 1 and 3 were developed as a serological diagnostic tool for pemphigus. Patients with pemphigus foliaceus show only anti-desmoglein 1 IgG autoantibodies, while patients with mucosal dominant type of pemphigus vulgaris have only anti-desmoglein 3 IgG. Finally, patients with the mucocutaneous type of pemphigus vulgaris have both anti-desmoglein 3 and anti-desmoglein 1 IgG. ELISA is a powerful and objective assay that allows easy screening of large numbers of sera to characterize patients for diagnosis and research purposes.

In general, ELISA antibody titers fluctuate in parallel with the disease activity with time in any particular patient, while the titers do not necessarily reflect the disease severity among different patients. This discrepancy is because patients’ sera are polyclonal containing both pathogenic and non-pathogenic antibodies for blister formation, as demonstrated by isolation...
of monoclonal antibodies from mice and humans. Such pathogenicity, or the lack thereof, can be measured in neonatal mice, in skin organ culture or in keratinocyte dissociation assays of cultured human keratinocytes.

Pathophysiology of blister formation in pemphigus

There are two major, not necessarily exclusive, theories of how pemphigus antibodies cause blisters. One theory is that antibodies cause steric hindrance of the desmoglein adhesion site thus interfering directly with adhesion. The other theory is that antibodies cause intracellular signaling that leads to loss of adhesion.

Pemphigus antibodies cause steric hindrance

Epitope mapping of pemphigus autoantibodies and monoclonal antibodies from mice and humans has demonstrated that pathogenic antibodies bind to the amino-terminal extracellular domain of desmogleins that is predicted to form the trans-adhesive interface between cells, based on the crystal structures of classic cadherins, molecules in the same gene family as desmogleins. In addition, pathogenic pemphigus foliaceus monoclonal antibodies cloned from patients bind to the mature desmoglein 1 which reveals the active adhesion site only after the proprotein is cleaved, but not to the proprotein which does not form the adhesion site. So-called “knockout mice” lacking desmoglein 3 show similar, if not identical, acantholytic lesions mimicking the phenotype of mucosal dominant type of pemphigus vulgaris. These mice show that lack of function (i.e. adhesion) of desmoglein 3, without antibody-induced signaling (e.g., by crosslinking a cell surface receptor), show the typical histology of pemphigus vulgaris. Desmoglein compensation theory logically explains the site of blister formation in the skin and mucous membranes in patients with pemphigus, suggesting blisters are formed as a result of the loss of adhesive function of each desmoglein isoform. If antibody signaling caused loss of adhesion, then one would expect that whenever antibodies bound desmoglein 3 a blister should result because of the resultant signaling, yet in fact this is not the case wherever desmoglein 1 is also present. These observations suggest that pemphigus blisters are initially caused by steric hindrance and not by the activation of a signaling pathway that causes the initial loss of adhesion, although such signaling may occur after loss of adhesion and may amplify the initial loss of cell adhesion. Furthermore, these data do not negate that modulation of signaling pathways that control desmosome stability could be useful in counteracting pemphigus antibody-induced loss of adhesion.

Pemphigus antibodies cause intracellular signaling

On the other hand, when pathogenic pemphigus antibodies bind to the keratinocyte cell surface, several signaling events have been shown to take place. The most widely studied are those pathways that involve p38 mitogen-activated protein kinase (p38MAP kinase) and plakoglobin. The most general indication of signaling is that pemphigus antibodies cause protein phosphorylation changes in keratinocytes. Studies of these changes indicated that p38MAP kinase was a major pathway stimulated by both pemphigus vulgaris and pemphigus foliaceus autoantibodies. These pathways may be activated only after cells lose their adhesion, but, even so, they probably increase the acantholytic effects of pemphigus antibodies, and blocking them may improve disease (see below). Another observations
regarding signaling in pemphigus was that keratinocytes genetically engineered to lack plakoglobin were not as susceptible to pemphigus antibodies as were wild type cells. This observation led to a pathway involving c-myc, which was shown to be elevated in pemphigus antibody-stimulated keratinocytes.

Some of these signaling pathways are probably involved in normal homeostasis of desmosomes and their components, such as transport to the cell surface, into the desmosome, and internalization. Pemphigus antibodies may act through modulation of these physiologic pathways. For example, as a result of signals induced by pemphigus antibodies that cause loss desmoglein adhesion as desmogleins reach the cell membrane, desmogleins may be depleted first from the cell membrane thereby decreasing or eliminating the pool of desmogleins for their incorporation into desmosomes, ultimating resulting in depletion of desmogleins in desmosomes leading to desmosome dysfunction (i.e. acantholysis). Although it is difficult at this time to determine which are the most critical signaling pathways contributing to pathogenicity, signaling pathways may be an important target in designing therapy for pemphigus in the future (see below).

Immunology of development of anti-desmoglein antibodies

Why do patients with pemphigus produce harmful autoantibodies against desmogleins? This is an ultimate and fundamental question that we need to answer in the future. To begin to address this question, upstream events of pathogenic antibody production have been investigated. It is probable that both anti-desmoglein B cells and desmoglein-peptide specific T cells that provide help to those B cells are necessary for anti-desmoglein antibody formation. In support of this model, circulating B cells producing anti-desmoglein 3 antibodies were detected by enzyme-linked immunospot (ELISPOT) assay in patients. Circulating T cells reacting with desmoglein 3 were detected in patients, but perhaps surprisingly, were also detected in normal people. To investigate the formation of anti-desmoglein antibodies in an animal model, an active disease mouse model for pemphigus vulgaris was developed by adoptive transfer of lymphocytes from desmoglein 3 deficient mice to immune-deficient desmoglein 3-expressing mice. This model was used to isolate anti-desmoglein 3 pathogenic monoclonal antibodies as well as desmoglein 3-specific T cells that help B cells to produce pathogenic antibodies. Both the T and B cells were needed for antibody formation. Aire (autoimmune regulator, a transcription factor) was also shown to play a role in regulating desmoglein 3 expression in the medullary thymic epithelial cells and in selection of T cells in thymus. Presumably expression of desmoglein 3 in thymus helps provide tolerance to that antigen in most people.

To further clarify the mechanisms for central and peripheral tolerance to desmoglein 3-reacting T cells and B cells will be an important step to develop antigen-specific immunosuppressive therapies.

Desmogleins are targets in infectious diseases

The story of the identification of desmoglein 1 as the target of staphylococcus exfoliative toxin (Table 1) illustrates the importance of having physicians as scientists.
The blisters in bullous impetigo and staphylococcal scalded skin disease have been known for many years to be caused by a toxin made and secreted by staphylococcus aureus, called exfoliative toxin. In bullous impetigo, the toxin is produced locally, causing blisters at sites of infection. In staphylococcal scalded skin syndrome, which usually is seen in infants or very young children, the toxin circulates and causes blisters distant from sites of infection. When injected into mice this toxin causes blisters. However, for many years after its discovery, it was not clear how this toxin caused blisters in the epidermis. Even after the toxin was molecularly cloned and shown to have the structure of a serine protease (i.e. a protease with a serine in its active site) that seemed to need a specific substrate in order to orient its catalytic site to be active, that substrate could not be identified. Ultimately, it was dermatologists, with their knowledge of skin diseases, who were able to solve this longstanding puzzle.

Even as early as the 18th century, astute clinicians who were superb morphologists (probably because they had little technology beyond their eyes and ears) recognized that staphylococcal scalded skin syndrome resembled pemphigus. Because of this observation, staphylococcal scalded skin syndrome was sometimes called “pemphigus neonatorum”. In addition, it was known that injection of exfoliative toxin into neonatal mice caused blisters whose histology was identical to that resulting from injection of pemphigus foliaceus antibodies into mice. In fact, any practicing dermatologists knows that whenever a biopsy of a patient with pemphigus foliaceus is taken, the report always indicates that although the histology is consistent with pemphigus foliaceus it is also consistent with bullous impetigo or staphylococcal scalded skin syndrome. Once it was learned that pemphigus foliaceus was caused by antibodies against desmoglein 1, it was a small step in logic to hypothesize that exfoliative toxin’s protein substrate might be desmoglein 1. In both cases the function of desmoglein 1 would be impaired with similar resultant histology.

In fact, that simple but eloquent hypothesis was shown to be correct. Exfoliative toxin was shown to cleave one peptide bound in one substrate, desmoglein 1 (Figure 4). The use of this toxin to enhance staphylococcus pathogenicity and infectivity is beautiful in its simplicity. Essentially, staphylococcus has evolved to produce a toxin that targets one peptide bond of one molecule to enable it to grow under the stratum corneum (the barrier of the skin), but enables it to be superficial enough so that when one child touches another the bacteria can be passed on.

Adenovirus provides another example of desmoglein involvement in infection. Most of human adenoviruses (serotypes A to F) use the coxsackie adenovirus receptor as a primary attachment receptor. However, serotype B adenovirus, which cause respiratory and urinary tract infections, does not use this receptor, but has recently been found to bind to desmoglein 2 as the primary high-affinity receptor (Table 1). Adenovirus binding of desmoglein 2 triggers an epithelial-to-mesenchymal-like transition, leading to transient opening of intercellular junctions and penetration of virus into the subepithelial cell layers and the blood stream, allowing the virus to spread.
Desmogleins are targets in genetic diseases

Mutations in genes encoding desmogleins have also been described in skin, hair, as well as heart diseases (Table 1). Striate palmoplantar keratoderma, an autosomal dominant disorder, is characterized by longitudinal hyperkeratotic lesions on the palms associated with focal or diffuse thickening of the plantar skin. Haploinsufficiency mutations in the gene for desmoglein 1, desmocollin 2, or desmoplakin, have been shown to underlie this skin disorder. Mutations in the gene encoding desmoglein 4 cause localized autosomal recessive hypotrichosis in humans and the lanceolate hair phenotype in mice. More recently, it has been discovered that arrhythmogenic right ventricular cardiomyopathy, which is clinically characterized by right ventricular enlargement and dysfunction, fibrofatty replacement of myocytes in the right ventricle, characteristic electrocardiographic abnormalities, ventricular arrhythmia, and sudden death, is caused by mutations in the genes for desmoglein 2, desmocollin 2, plakoglobin, plakophilin 2, or desmoplakin. These genetic findings underscore the importance of desmoglein (and other desmosomal molecules) mediated adhesive function in tissue integrity and function.

Desmogleins do more than provide adhesion of cells

Experiments showing that misexpression of desmoglein isoforms where they are not normally present causes differentiation defects indicate that desmogleins may do more than simply provide adhesion. For example, desmoglein 3 expression in the superficial epidermis, where it is not normally present, cause abnormal epidermal differentiation and stratum corneum formation with increased transepidermal water loss. In mice with a genetic deletion of desmoglein 2 there is a defect in blastocyst proliferation resulting in failure of implantation. Conversely, forced expression of desmoglein 2 in the superficial epidermis causes increased proliferation. The above findings indicate profound effects of desmogleins on keratinocyte proliferation and differentiation. Presently, it is thought that these effects are produced through signal transduction pathways, although the exact pathways have not been elucidated. One major contributor to signaling through desmosomes may be plakoglobin. As discussed above, desmogleins bind to plakoglobin, which is related to β-catenin, a well characterized molecule important in the Wnt signaling pathway. This pathway is important in proliferation and differentiation as well as embryological development. Amount and isoforms of desmoglein may control amount of free plakoglobin that could contribute to signaling. However, much work needs to be done in the future to link signaling to specific molecules and pathways.

Further evidence indicating that desmogleins do more than just provide cell adhesion are the observations that demonstrate that desmoglein 1 is critical for proper stratification and differentiation of epidermis. Interestingly, this effect, which is associated with down regulations of the EGFR-Erk1/2 signaling pathway, requires neither extracellular adhesion nor intracellular plakoglobin binding. These results implicate pathways independent of plakoglobin in desmoglein signaling.
The future: therapy of pemphigus based on the understanding of its pathophysiology and immunology

Anti-idiotypic therapy

Recent genetic analysis of monoclonal antibodies cloned from pemphigus vulgaris and foliaceus patients indicates that both pathogenic and non-pathogenic monoclonal antibodies are found, and that there are a limited number of parenteral B cell clones for these antibodies. A limited set, but several different, immunoglobulin variable heavy chain genes are used in patients to make pathogenic antibodies, therefore, it probably is not possible to target variable heavy chains to treat disease. However, when the complementarity determining region 3 (CDR3) of the antibodies was analyzed, pathogenic antibodies shared a common sequences. (The CDR3 region of antibodies is thought to be the major region that binds the corresponding antigen). Randomization and site-directed mutagenesis of the heavy chain CDR3 sequences in some of these antibodies illustrated the importance of only a few, or even one, amino acids for binding and/or pathogenicity. Such data suggest that it might be possible to target common sequences in the CDR3 regions of pathogenic pemphigus antibodies to prevent disease. Reagents derived from phage display cloning of monoclonal antibodies from patients could be used to screen for such blockers.

Rituximab

From knowledge that pemphigus is an autoantibody-mediated disease with a limited set of anti-desmoglein non-tolerant B cells, as discussed above, it makes sense that eliminating B cells might improve disease, especially if these non-tolerant set of B cells cannot come back after B cell depletion. In fact, the success of rituximab for therapy tends to validate this idea. Rituximab is an anti-CD20 antibody. CD20 is found on all mature B cells, but not the stem B cells. B cell pools are re-populated from stem B cells (i.e. B cells that have not formed immunoglobulins against specific antigens). Rituximab should, therefore, in theory, eliminate anti-desmoglein B cell clones.

In fact, rituximab has shown excellent results in treating pemphigus patients refractory to standard therapy (e.g. prednisone plus immunosuppressives like azathioprine or mycophenolate mofetil). A single cycle (2 injections over 2 weeks or 4 injections over a month) can lead to complete remission is over 80% of patients, although some relapse and some may need low dose prednisone therapy. Rituxan causes a profound depletion of circulating B cells, but presumably does not deplete plasma cells, which do not have CD20 on their surface. Since in most patients anti-desmoglein antibodies go down after rituximab therapy, the anti-desmoglein antibody-producing plasma cells may be short-lived and need frequent replenishment by B cells.

In any case, elimination of circulating B cells has proven to be excellent therapy for patients with refractory pemphigus.

Signaling

As discussed above, pemphigus antibody binding to desmoglein on the keratinocyte cell surface causes signal transduction which can exacerbate acantholysis. Therefore, if the right
signaling pathways can be identified then pharmacologically interrupting them might be beneficial in patients. For instance, blocking the p38MAP kinase pathway in a mouse model of pemphigus has been shown to modulate disease.

In addition, studies, discussed above, have shown that the normal system of cycling of desmosomal components may be interrupted in pemphigus, causing depletion of desmoglein in desmosomes with subsequent acantholysis. Tools might be found to perturb signaling to affect this physiologic process in order to increase desmoglein synthesis and subsequent incorporation into desmosomes, thereby, stabilizing them and counteracting the depletion induced by pemphigus antibodies. It may be that corticosteroids, which are already known to be very effective in therapy, act by this precise mechanism, in that they increase desmoglein synthesis through signaling.

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Figure 1.
One of the major pieces of evidence that desmoglein 1 is the pemphigus foliaceus antigen. 2-dimensional gel electrophoresis of extracts of epidermis followed by immunoblotting with pemphigus foliaceus serum and an anti-desmoglein 1 antibody shows that both identify spots with the same migration, convincing proof that both bind the same protein. (From, Koulu, L., Kusumi, A., Steinberg, M.S., Klaus Koytun, V., and Stanley, J.R. 1984. Human autoantibodies against a desmosomal core protein in pemphigus foliaceus. J. Exp. Med. 160:1509–1518).
Figure 2.
Original data from the cloning of pemphigus vulgaris antigen. A) Purified λgt11 expression phage that contain cDNA for pemphigus vulgaris antigen. A single clone multiplies in bacteria, and all its offspring were blotted to nitrocellulose. All resultant clones stain positively with pemphigus vulgaris sera. The cDNA was sequenced to show that the protein produced was desmoglein 3. B) John Stanley (left) and Masayuki Amagai on the day in 1991 when the pemphigus vulgaris antigen clone was identified. (Amagai, M., Klaus-Kovtun, V., and Stanley, J.R. 1991. Autoantibodies against a novel epithelial cadherin in pemphigus vulgaris, a disease of cell adhesion. Cell 67:869–877.)
Figure 3.
A monoclonal, monovalent anti-desmoglein 1 antibody cloned from a pemphigus foliaceus patient causes typical histology of pemphigus foliaceus when injected into normal human skin organ culture.
Figure 4.
Coomassie blue gel showing cleavage of the 84-kD extracellular domain of desmoglein 1 to a 50 kD and 34 kD fragment, increasing with time of incubation with exfoliative toxin A. (Hanakawa, Y., Schechter, N.M., Lin, C., Nishifuji, K., Amagai, M., and Stanley, J.R. 2004. Enzymatic and molecular characteristics of the efficiency and specificity of exfoliative toxin cleavage of desmoglein 1. *J. Biol. Chem.* 279:5268–5277.)
Table 1

Desmogleins targeted in human diseases

| Isoform     | Type          | Diseases                                                                 |
|-------------|---------------|--------------------------------------------------------------------------|
| desmoglein 1| autoimmune    | pemphigus foliaceus                                                     |
|             |               | pemphigus vulgaris (mucocutaneous type)                                  |
|             |               | paraneoplastic pemphigus                                                 |
|             | infection     | staphylococcal scalded skin syndrome                                     |
|             | genetic       | striate palmoplantar keratoderma                                          |
| desmoglein 2| infection     | respiratory and urinary tract infection (receptors for adenovirus serotypes 3, 7, 11, and 14) |
|             | genetic       | arrhythmogenic right ventricular cardiomyopathy                           |
|             |               | dilated cardiomyopathy                                                   |
| desmoglein 3| autoimmune    | pemphigus vulgaris (mucosal dominant type, mucocutaneous type)           |
|             |               | paraneoplastic pemphigus                                                 |
| desmoglein 4| genetic       | hypotrichosis                                                            |