REGIONAL VARIATIONS IN ANTIGENIC PROPERTIES OF SKIN
A Possible Cause for Disease-specific Distribution of Skin Lesions

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A remarkable feature of many skin diseases is that each affects distinct sites on the body. The patterns are sufficiently characteristic and reproducible to be a major clinical feature used to diagnose dermatologic diseases (1, 2). Unfortunately, the cause for these differences is mostly unknown. One intriguing possibility is that the location of lesions in autoimmune disease involving skin is determined by regional variations in the expression of the target antigen(s).

To examine this possibility we have mapped the expression of two skin specific antigens, the pemphigus vulgaris (PV) and bullous pemphigoid (BP) antigens, in different regions of the body. These antigens are the targets of specific auto-antibodies that cause two skin diseases, pemphigus vulgaris and bullous pemphigoid, in which the distribution of cutaneous lesions is markedly different. The PV antigen is a 210 kD surface glycoprotein (3) synthesized by keratinocytes. Antibodies to this antigen are the cause of pemphigus vulgaris (4), a disease characterized by blisters that appear predominantly on the scalp, face, oral mucosa, and upper torso (1, 2). The BP antigen is a 220–240 kD glycoprotein (5) synthesized by epidermal basal cells (6, 7). Antibodies to this antigen are believed to cause bullous pemphigoid (8), a disease characterized by bullae that appear predominantly on the flexural surfaces of the body, and which spare the face and scalp (1, 2). Antibodies to PV or BP antigens are present in the serum and in the skin of most patients during the active phase of the respective disease, but are rare in normal individuals (8–10).

Materials and Methods

The expression of PV and BP antigens was assayed by indirect immunofluorescence, as previously described (11), in 46 specimens of normal human skin. The skin specimens were obtained by punch or excision biopsy from different areas on the body in different individuals, immediately frozen in liquid nitrogen, cut in 4-μm sections on a cryostat, and used within 1 wk. Each skin specimen was reacted with serial dilutions of three sera with high titers (>640) of PV antibodies, three sera with high titers of BP antibodies, and normal human serum. Antigen concentration was expressed as the highest dilution of serum (end-point titer) that stained the target antigen. This was determined independently by two investigators. The reading of both investigators was similar within one dilution.
Results and Discussion

The expression of PV and BP antigens in 46 specimens of normal human skin, measured by indirect immunofluorescence, was highly variable (Fig. 1, A–D). It ranged from undetectable levels (end-point titer of 0) to strong (end-point titer ≥1,280). Since a single serum of each specificity was used to assay all skin specimens, the variations were not due to differences in antibody levels in the serum. Nor were these differences due to day-to-day variation in the results of indirect immunofluorescence assays, since in preliminary experiments we found that there was only a twofold difference in end-point titer when replicate aliquots of the same serum were tested repeatedly on the same or on different days against replicate sections of the same specimen of skin. The most likely explanation for the differences in result is that there were variations in antigen expression in the different tissue specimens studied.

To examine whether the variation in antigen expression was random or influenced by the site of origin of the skin, the results were reexamined after the skin specimens had been grouped according to their location on the body. The results obtained for PV antigen are presented in Fig 2. The expression of this antigen in normal skin obtained from the same anatomic region was relatively similar (on average, within one dilution), whereas it varied markedly (over seven dilutions) in skin obtained from different sites. The causes for the usually small
Regional variation in expression of PV antigen in normal human skin

Variations in PV antigen expression in skin obtained from similar anatomic regions probably include intrinsic limits on the reproducibility of the immunofluorescence assays, which, as noted above, can lead to twofold dilution differences in end-point titer, and possibly to small differences in antigen expression between individuals. In addition, the large anatomic areas used to group the data may not match exactly the actual pattern of antigen expression over the epiderm. Consequently there may be some variation in antigen expression within each of these arbitrarily selected regions. We believe the latter is the explanation for the large variation in antigen expression in skin obtained from the chest and abdomen, which includes areas that are commonly (upper chest) and rarely (abdomen) involved in pemphigus.

The amount of PV antigen in different regions on the body was expressed as the average end-point titer obtained when three sera with PV antibodies were reacted with all skin specimens obtained from the same region. As shown in Fig. 3, PV antigen was strongly expressed in axilla, scalp, buccal mucosa, face, and neck; areas commonly involved with lesions in pemphigus vulgaris (1, 2). 21 skin specimens obtained from these sites were tested. All expressed PV antigen in amounts yielding average end-point titers of 396–499. In contrast, expression was low in the groin and lower back, areas rarely affected by pemphigus. Six specimens were tested from these sites. No PV antigens could be detected in two (33%). In the remainder, high concentrations (end-point titer <50) of PV antibodies were required to detect the antigen, indicating that little was present. Expression was intermediate in the other areas of the body studied, which are occasionally affected by PV. These variations were not solely due to differences in antigen concentration between individuals, since the expression of PV antigen in similar regions in different individuals was relatively constant. Nor were they due to PV antigen heterogeneity (12), since the variations persisted when the same serum was used to assay all specimens (see Fig. 2).

To examine whether the cause for the regional variation in expression of PV antigen is one that affected equally all antigenic properties of skin, or affected this antigen selectively, we measured concurrently the expression of another skin-specific antigen, the BP antigen, in all skin specimens. As shown in Fig. 3,
there was marked regional variations in the expression of BP antigen. There was no correlation between the pattern of expression of PV and BP antigens. Scalp, which strongly expressed PV antigen, expressed little BP antigen. Conversely, expression of BP antigen was high in the groin and back, which expressed little PV antigen. The independent variation in expression of the two antigens, when measured concurrently in the same specimens of skin, indicate their expression is under separate control. As with PV antigens, there was an overall correlation between expression of BP antigen and location of lesions in this disease. Expression was high in areas commonly involved with lesions in bullous pemphigoid (groin, axilla [1, 2]), very low in areas that are rarely involved (scalp, face, neck), and variable in other areas (torso, extremities), which are less consistently involved.

The results of these studies indicate that: (a) There are marked regional variations in the antigenic properties of skin. (b) Different epidermal antigens have different patterns of expression, indicating that their expression is under separate genetic or environmental control. (c) There is a correlation between the
expression of some epidermal antigens and the distribution of lesions in autoimmune skin disease involving these antigens. The results provide a previously unavailable explanation for the distribution of skin lesions in pemphigus vulgaris and bullous pemphigoid, and in general suggest that regional variations in the antigenic properties of skin may be one of the factors that determines the location of lesions in cutaneous diseases.

Summary

The possibility that the distribution of skin lesions in some cutaneous diseases is due to variations in the antigenic properties of skin was investigated by mapping the expression of the skin-specific pemphigus vulgaris and bullous pemphigoid antigens in different regions of the body. The expression of both antigens was relatively stable within the same region, but varied between regions in a pattern that was distinct for each antigen. For each antigen there was a correlation between regions of high expression and location of skin lesions in autoimmune diseases involving the antigen. The results indicate that there are marked regional differences in the antigenic properties of skin and suggest this may influence the distribution of cutaneous lesions in some skin diseases.

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