Immunohistochemical Demonstration of Immunoglobulin A in Human Sebaceous and Sweat Glands

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Immunoglobulin A (IgA) mediated humoral defense mechanisms have been detected on all mucous membrane surfaces. There are only a few papers about the presence of IgA in human skin. In order to demonstrate the occurrence of IgA in sebaceous and sweat glands, biopsies of normal human skin were investigated and compared to intestinal mucosa. Two different commercially available anti-IgA antibodies were used. For light microscopy peroxidase-anti-peroxidase (PAP) or avidin-biotin complex (ABC) staining was used, and for electron microscopy protein-A-gold (PAG) labeling was performed on tissue sections. Specifically decorated IgA was found in sebaceous glands as well as in various portions of eccrine glands. In sebaceous glands, the maximum of IgA concentration was seen near the mouth of pilosebaceous ducts. Sweat ducts exhibited a continuous coat of IgA, whereas secretory portions contained only singular scattered IgA positive cells. Immunoelectron microscopy suggests endocytotic uptake and processing of IgA in the glandular cells. These results indicate strongly that IgA are secreted by normal human sebaceous and sweat glands. Because it is well known that IgA plays an important role in inactivation of invading viruses, bacteria, and other antigenic structures on mucous membranes, it appears that IgA in sebum and sweat fulfil a similar function on the outer body surface. *J Invest Dermatol 91:13–17, 1988*

M any of the skin's non-immunologic [1] and immunologic [2] functional properties serve as protective principles of the body surface. During the last decade, interests were mainly focused on the cellular part of the skin immune system. Streilein [3–5] proposed the term "SALT" for a skin-associated lymphoid tissue in analogy to established mucous membrane systems. He assumed that this system consisted of Langerhans cells, recirculating T lymphocytes, keratinocytes, and a set of draining lymph nodes. Bos and Kapsenberg [2] extended this concept to other cellular elements and suggested a multicellular skin immunity system (SIS).

In addition to the cellular constituents of SIS, humoral components are also relevant. Immunoglobulin-mediated humoral defense mechanisms have been detected on all internal body surfaces [6,7]. The mucosa associated lymphoid tissue (MALT) is capable of local production of immunoglobulin A (IgA) [8]. A number of plasma cells in the lamina propria of the gut [9], bronchus, conjunctiva, and genitourinary tract, or in the mammary and salivary glands produce IgA dimers, which are released and bound to the secretory component (SC) of epithelial cells [10]. After endocytosis, the SC-IgA complex is further processed and secreted into the lumen where it covers the respective surfaces [11–13]. IgA is able to inactivate bacterial, viral, mycotic, or even other antigenic material [14] and inhibit their invasion. Polio and rubella vaccination; resistance against rhinovirus; neutralization of toxins, e.g., of Vibrio cholerae [6]; inhibition of colonization with Streptococci [15], Staphylococci [16], Gonococci [17], or of absorption of milk and food antigens [18] reflect the clinical relevance of mucosal immunity.

In view of the importance of the skin as a protective organ, surprisingly few data have been reported about similar mechanisms in human epidermal structures. Kaneko et al [19,20] reported on sporadic IgA and SC positive areas in human epidermis and in eccrine glands. Lai A Fat et al [21] observed only immunoglobulin positive lymphocytes and plasma cells in the dermis. Tourville et al [22] detected the occurrence of SC in the eccrine glands, but no IgA there. Recently, our group presented preliminary data about the presence of IgA in human sebaceous glands [23]. Although the presence of IgA has been demonstrated biochemically in human sweat [24] and earwax [25], determination of IgA gave only inconclusive results in extracts of comedones [26].

Nevertheless, biochemical analysis of sweat and sebum can neither reveal the normal in situ situation nor elucidate the mode of a tentative IgA production and secretion. Therefore, light and electron microscopic immunohistochemical studies were designed in order to study the assumed presence and distribution of IgA in normal cutaneous tissue. The results were compared to the secretory mechanism of IgA in the intestinal epithelium.

MATERIALS AND METHODS

Tissue Processing Samples of normal human skin from five male surgery patients ranging in age from 16–78 years with a mean of 46 years from different regions (forehead, shoulder, breast, back) were obtained under local or general anesthesia. In all cases electrophoresis and immunoglobulin levels including IgA were within normal range. Intestinal mucosa from the jejunum was obtained from a patient who was undergoing gastrectomy for peptic ulcer disease. One part of each specimen was immediately fixed in 7% buffered paraformaldehyde, dehydrated, and embedded in paraplast. The other part was cut into small pieces and fixed in a mixture of 4% paraformaldehyde and 0.5% glutaraldehyde in phosphate-buffered (0.01 M, pH 7.4) isotonic saline (PBS, Sigma, Munich, FRG) for 4 h. After four rinsing steps in PBS the specimens were dehydrated in ethanol, embedded in LR-White (London Resin Comp. Lt., Woking, England) and polymerized at 60°C. A skin biopsy from a 17-year-old patient suffering from X-linked infantile agammaglobulinemia Bruton was routinely embedded in parablast for control purposes.

Immunohistochemistry

Light Microscopy 10-μm-thick paraffin sections were deparaffinized in xylene and washed in 1% methanolic hydrogen peroxide for 30 min in order to block endogenous peroxidase activity. After PBS rinsing and 10-min preincubation with 4% ovalbumine (Sigma) specimens were incubated for 2 h with two different, Elisa tested, rabbit anti-human IgA (α-chain) antibodies diluted 1 : 200 in PBS (Calbiochem Behring, San Diego, CA) and 1 : 50 (Dako, Glostrup, Belgium), respectively. The sections were subjected to the Avidin-biotin-complex (ABC) technique as described by Hsu [27] using the following reagents: phosphate-buffered isotonic saline (PBS; Sigma), biotinylated goat-anti-rabbit-antibody (diluted 1 : 300; Amersham, Little Chalfont, England), peroxidase labeled avidin (diluted 1 : 70; Sigma), 0.01% hydrogen peroxide, 3,3-diaminobenzidine (DAB, 0.05%; Serva, Heidelberg, FRG). Sections were counterstained with hematoxylin.

Semithin sections [1–2 μm] of resin embedded material were cut with glass knives on an ultramicrotome (Reichert, OMU2). After air drying, a modified double bridge Peroxidase-anti-Peroxidase method as described by Vacca [28] was used. Preincubation (15 min) with 1% methanolic hydrogen peroxide was followed by careful washing in PBS (3 times for 5 min each), incubation for 10 minutes with 4% ovalbumine, and then with the rabbit anti-human IgA antibody (diluted 1 : 100 in PBS; Calbiochem-Behring) for 12 h. Once the slides were treated with swine anti-rabbit sera (diluted 1 : 20; Dako) and peroxidase-rabbit-anti-peroxidase reagent (diluted 1 : 10; Dako) each for two hours, these two incubation steps were repeated consecutively. Then the peroxidase molecules were visualized by hydrogen peroxide (0.01%)-DAB reaction (0.05%; Serva). Rinsing in PBS between the incubation steps was performed thoroughly. Semithin sections were counterstained with toluidine blue. Light microscopic investigations and photography were performed using a Reichert Univar microscope.

Electron Microscopy Ultrathin sections (grey to silver) were cut on a Reichert OMU 2 ultramicrotome by diamond knives and mounted on uncoated gold grids.

Preincubation of the ultrathin sections with millipore filtered 4% ovalbumine for 10 min was followed by overnight incubation with rabbit IgA antibody (diluted 1 : 400 in PBS; Calbiochem-Behring). The grids were then rinsed in PBS and the antigen-antibody reaction site visualized with a protein-A gold (PAG) technique (29) using 15-nm gold particles (diluted 1 : 50 in PBS; Janssen, Beerse, Belgium). After final PBS rinsing and short air drying, ultrathin sections were counterstained with uranyl acetate and examined in a Zeiss EM 9 or a Jeol 100 S electron microscope.

Controls Controls for light and electron microscopy included dilution series [comprising a wide range (1 : 30 up to 1 : 2000)] and omission of the anti-IgA antibody, replacement of the antisera by diluted non-immune sera, and inactivation of the anti-IgA antibody by preincubation with normal human serum. Beyond that, the specificity of the immunogold labeling was assessed by application of pAG alone and by incubation with non labelled protein A before pAG application.

RESULTS

Light Microscopy Investigation of paraffin and semithin LR-White sections revealed specific binding of the immunoreactants in sweat glands, sebaceous glands, plasma cells, and lumina of blood vessels. No variations could be observed in the specimens taken from the different regions.

In the sweat glands brownish precipitates were coating the luminal surfaces of many, but not all dermal ducts (Fig 1a). In some of the secretory portions the ducts and intercanaliculi between the secretory cells were positive, preferentially at the luminal borders (Fig 1b). Few scattered cells in these portions showed positive cytoplasmic staining (Fig 1b).

Sebaceous glands were poorly preserved in paraffin sections and only faint positivity could be demonstrated. In semithin sections well-preserved sebocytes revealed distinct peripheral cytoplasmic staining, sparing the lipid vacuoles (Fig 2a). Staining density increased concomitantly with progressive differentiation of sebocytes. The most intensive reaction appeared to be present at the opening of the glandular acini into the pilosebaceous duct within a mixture of horny lamellae and positive dissolving sebocytes (Fig 2a).

Lumina or inner surfaces of many blood vessels showed homogenous brown DAB precipitates intermingled with negative erythrocytes. In the investigated biopsies, plasma cells were very rare and randomly scattered in the dermis, but strongly positive. Keratinocytes, hair follicles, connective tissue structures, and controls were consistently negative. In the specimen taken from the patient with agammaglobulinemia labeling for IgA could not be detected in any of the cutaneous glands or blood vessels.

Electron Microscopy In general, a similar distribution of IgA could be demonstrated by PAG labeling.

In sweat glands gold granules decorated the luminal surfaces of ducts and more intensely the microvilli of the secretory coils. The narrow intercanaliculi contained tracer particles coating the lumina (Fig 1c). Intracytoplasmic deposition of gold granules adjacent to characteristic dense granules could be found in some mucous cells. In contrast, all serous cells were negative (Fig 1c).

In sebaceous glands gold particles showed linear arrangement along intercellular spaces between sebocytes (Fig 2b). Intracytoplasmic protein A gold labeling could be observed in all suprabasal differentiated sebocytes, but not in undifferentiated basal sebocytes. In close relation to the cell membranes and within the cytoplasm, sparing the lipid vacuoles, local granular accumulation of gold granules was detected (Fig 2b). In terminally differentiated cells near the mouth of the glandular acini this patchy aggregation disappeared and a more diffuse intense staining was found (Fig 2c). Keratinocytes of sebaceous ducts, infundibuli, and hair follicles were negative.

Blood vessels revealed irregular positivity in their lumina. Plasma cells were not detected in the dermis. Interstitial compartements and fibroblasts were negative.

The lamina propria of jejunal mucosa revealed numerous plasma cells, most of which displayed staining for IgA. Gold granules decorated cisternae of the rough endoplasmatic reticulum and saccules associated with the golgi complex of plasma cells. Columnar epithelial cells in gland crypts of Lieberkühn could be demonstrated to react with greater density than villous epithelium. Tracer particles were found in the interstitium near the epithelium, on basal and partly on lateral plasma membranes of columnar cells, and in many cytoplasmic vesicles, preferentially in apical position and in close relation to cell membranes. In addition, microvilli and luminal mucus were labeled. Goblet cells and other mucosal cell types were unstained.
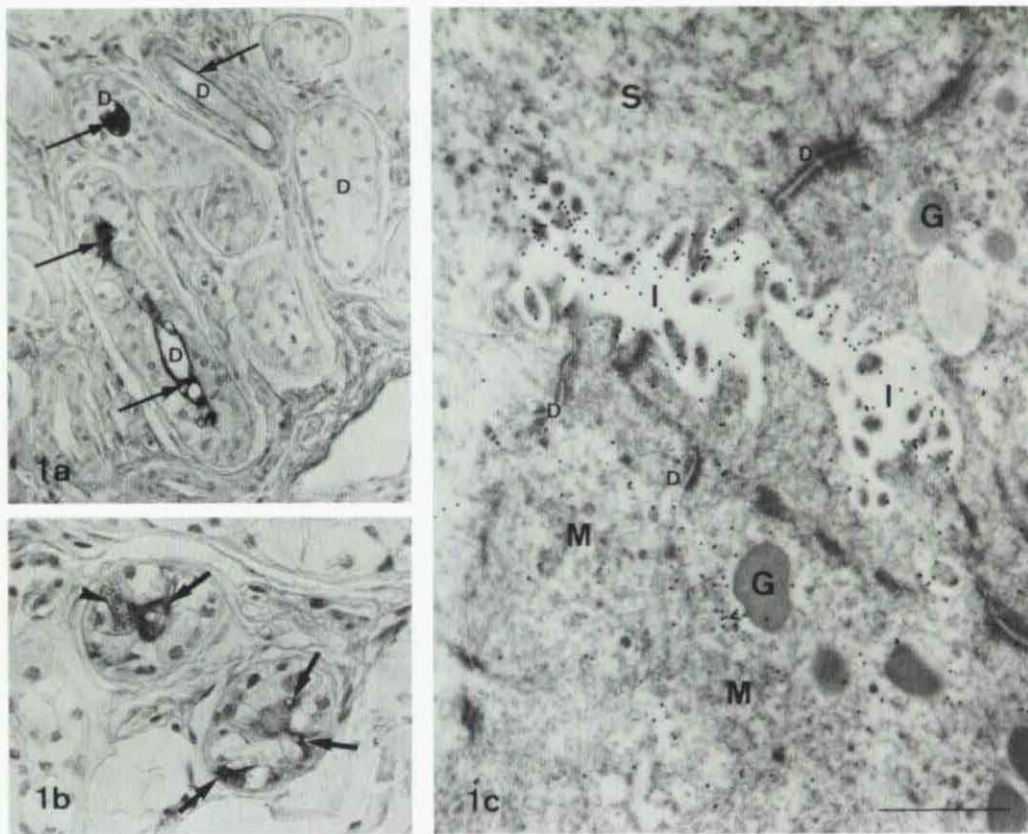
Figure 1. Immunostaining of sweat glands and ducts *(a,b)* with anti-IgA-antibodies using ABC method on paraffin sections and *(c)* PAG labeling on ultrathin sections. *a*: Some lumina of sweat ducts *(D)* are intensely stained *(arrows)*, preferentially at their luminal surfaces. Hematoxylin, ×250. *b*: Intercanaliculi and ducts of secretory portions contain DAB precipitates *(arrows)*. Note the cytoplasmic staining of one secretory cell *(arrowhead)*. Hematoxylin, ×400. *c*: Intercanaliculi *(I)* reveal gold granules coating microvilli. Intracytoplasmic labeling clustering around dense granules *(G)* in mucous cells *(M)*. *S*: Serous cells; *D*: Desmosomes. Uranyl acetate, *Bar:* 1 μm

Controls Higher dilution of the antisera resulted in diminution of background staining. No non-specific reactions, but weaker positivity could be demonstrated at the lowest concentrations, even using gold labeling. All the other control experiments exhibited entirely negative results.

DISCUSSION

The results of our immunocytochemical studies indicate strongly that IgA are secreted by cutaneous eccrine and sebaceous glands. The minor attention paid to this fact by traditional immunodermatology can only partly be explained by interests sharply focused upon cell-mediated immune mechanisms. Most of the positive staining reactions in routine immunocytochemistry have probably been disregarded as unspecific fluorescence or as freezing artifacts in the usually poorly preserved sebaceous glands. However, using modified fixation procedures, methacrylate embedding, and different immunolabeling techniques, we were able to visualize anti-IgA-binding sites in skin appendages.

A possible loss of antigenic material during preparation procedures or IgA-antigen masking effects [30] cannot be excluded from our studies. Therefore, small amounts of IgA might still be present in the negative parts of sweat glands, basal sebocytes, or within lipid droplets, escaping our detection techniques.

Specificity of the methods used seems to be high. Both immunohistochemical reactions showed comparable results. Multiple controls, including omission of different steps of the staining procedure and absorption of the antibody by IgA containing human serum, were negative. Additionally, detection of IgA in plasma cells [9], intestinal epithelia [11], and in the serum of the blood vessels [31] in our specimens served as positive control. In the gut, the small number of unstained plasma cells [9] confirms the reliability of the immunohistochemical methods. Furthermore, the lack of staining for the anti-IgA antibody in the biopsy taken from a person with agammaglobulinemia underlines the significance of the staining procedures used.

The distribution of IgA in the various glandular portions seems of special interest. In sweat glands some dark mucous cells of secretory coils contained little IgA, whereas the clear serous cells were consistantly negative. Most of the intercanalicular and ductal lumina were strongly positive. This could reflect a sequence of events starting with IgA secretion by some functionally active mucous cells, collection of these secretions in intercanalicular lumina, and, finally, concentration of IgA in the proximal dermal duct.

In sebaceous glands minimal or no staining was observed in basal portions of the gland and poorly differentiated sebocytes. Linear intercellular arrangement and intracytoplasmic accumulation of tracer particles near cell membranes resembling coated pits indicates endocytosis of IgA. Maximal staining density was present at the transitional zone, where terminal sebocytes are discharged into the pilosebaceous duct. Again, this could reflect a dynamic concentration and excretion process.

Further support for such an endocytotic mechanism is provided by the demonstration of secretory component in human keratinocytes [19,32] and sweat glands [22]. Binding of IgA to secretory component expressed on cell membranes seems to occur predominantly on differentiating sebocytes and mucous sweat gland cells.

Demonstration of a similar vesicular arrangement of IgA in the intestinal epithelium strongly corroborates the concept of an active glandular secretion of IgA in human skin. Investigations showing a higher fractional concentration of IgA in relation to IgG in sweat than in sera [24] and extensive amounts of gold granules within
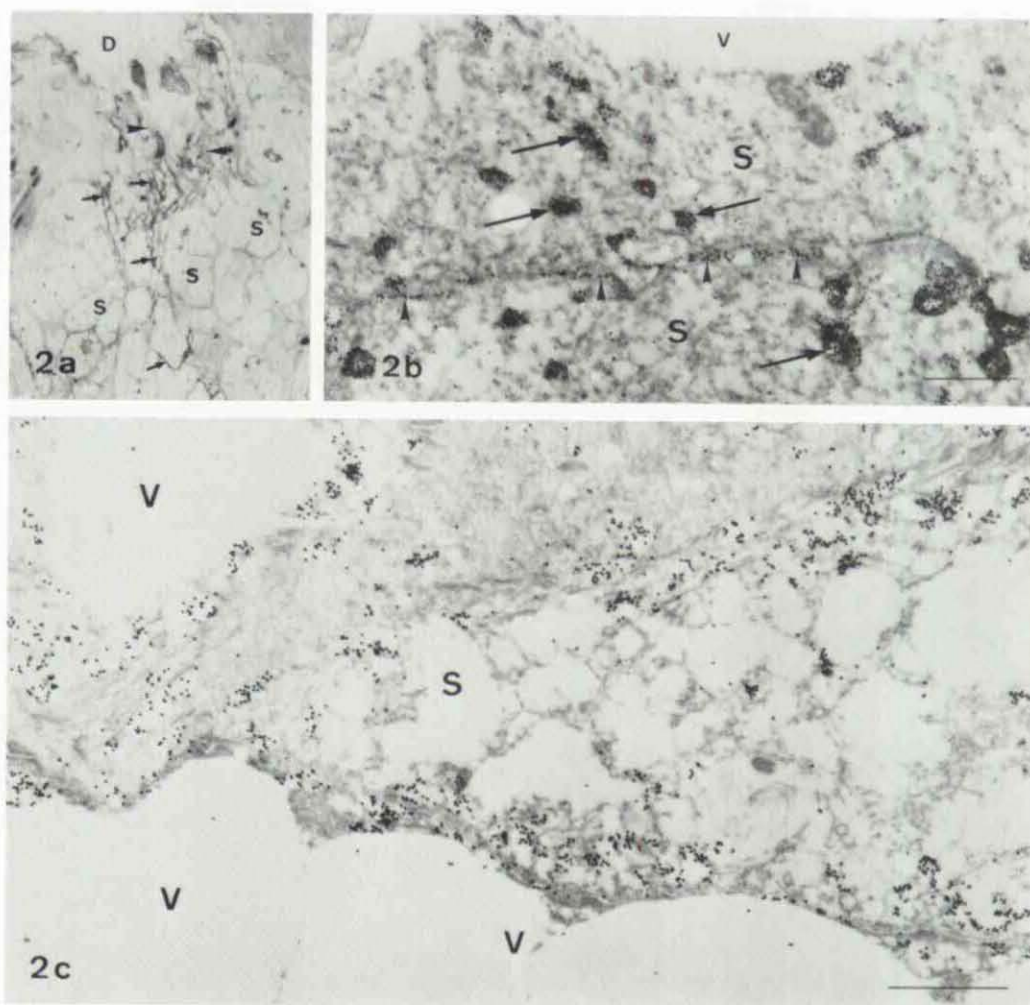
Figure 2. Demonstration of immunoglobulin A in sebaceous glands (a) light microscopically by modified PAP technique and (b,c) electron microscopically by PAG labeling. a: Sebocytes (S) reveal distinct peripheral cytoplasmic staining (arrows). Note the intense reaction near the pilosebaceous duct (D) between horny lamellae (arrowheads). Semithin section, toluidine blue, × 325. b: Linear arrangement of gold particles (arrowheads) within intercellular spaces between suprabasal differentiating sebocytes (S). Local granular accumulation of tracer particles (arrows) near the cell membranes and within the cytoplasm. V: Lipid vacuoles. Ultrathin section, uranyl acetate. Bar: 1 μm c: Higher differentiated sebocytes (S) contain more distributed and less accumulated gold granules sparing the large lipid vacuoles (V). Ultrathin section, uranyl acetate. Bar: 1 μm.

ductal lumina indicate a selective transport of IgA. Thus, only passive leakage of this immunoglobulin together with other serum components is very unlikely.

Nevertheless, the origin of IgA molecules cannot be elucidated from our studies. They could either be recruited from circulating plasma [31] or be locally secreted from periglandular B lymphocytes [33]. Especially near the periorificial locations and within inflammatory lesions these mechanisms could also be operative.

Our findings correlate well with present knowledge about the significance of IgA antibodies in other biologic secretions, such as saliva [34], colostrum [35], urine, or gastrointestinal fluid [8]. These antibodies possess antibacterial, antiviral, antimycotic, and even antitoxic activities [6,15,36] and thus represent a primary specific defense system against invading microorganisms and other antigenic material on all mucosal surfaces. It appears reasonable, therefore, that IgA antibodies in sebum and sweat fulfil similar functions on the outer body surface, thus contributing a humoral component to the complex immunologic cutaneous barrier system.

Several biologic or pathologic phenomena support such a concept of IgA-mediated cutaneous immunity. In the pilosebaceous region, where resident microbial flora is abundant, these organisms are usu-

ally not able to penetrate below the mouth of the sebaceous duct [37]. Thus, IgA antibodies might, in parallel to their activity in gastrointestinal epithelia [8], prevent their adhesion and/or penetration. Similar considerations could be true for sweat ducts, where IgA could be most useful in warding off microorganisms already at the surface.

Various forms of IgA-deficiency syndromes provide models for the clinical relevance of IgA secretion [38–41]. In many of the affected individuals, incidence of skin infections is markedly increased and patients suffer from folliculitis, furunculosis, and similar affections of bacterial, viral, or mycotic origin [38,40,41]. In some cases IgA-substitution resulted in remission of the disease [40].

Our observations on sweat glands indicate that only few cells of the secretory coils secrete IgA under physiologic conditions. However, in sebaceous glands higher differentiated cells were consistently positive. Considering the enormous number of sweat and sebaceous glands in skin, the total quantity of IgA excreted in sebum and sweat should be remarkable. This could well match the amount secreted by internal mucous membrane epithelia and thus play an important role in the complex immunologic defense system of the skin.

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