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Epidermal Ia Molecules from the *I-A* and *I-EC* Subregions of the Mouse *H-2* Complex

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Abstract. Immune response region-associated (Ia) antigens encoded by genes in the *I-A* or *I-EC* subregions have been detected on murine epidermal cells by indirect immunoprecipitation, using antisera produced against murine lymphoid cells. The Ia antigens encoded by genes in these subregions are composed of two polypeptides with approximate molecular weights of 33,000 and 28,000. The Ia antigens are not derived from contaminating B- or T-cell populations. The Ia molecules from lymphocytes and epidermal cells appear to have identical subunit structures and very similar, if not identical, molecular weights. The possible biological role of the Ia antigens on epidermal cells is discussed.

Introduction

The major histocompatibility or *H-2* complex of the mouse has been divided into five regions (*K*, *I*, *S*, *G*, and *D*). Genes in the *I* region are involved in regulating the immune response to antigens, graft-versus-host reactivity, T-B cell collaboration, and graft rejection (discussed in Shreffler *et al.* 1976, Klein 1975). Furthermore, *I*-region genes code for a set of serologically detected cell-surface alloantigens, designated Ia antigens. In the mouse, the *I* region has been subdivided into several subregions (*i.e.*, *I-A*, *I-B*, *I-J*, *I-E*, and *I-C*) by genetic mapping of immune response genes and by serological analysis of cell-surface antigens in recombinant strains of congenic mice (Schreffler *et al.* 1976, Murphy *et al.* 1976).

The Ia antigens isolated from mouse spleen cells by indirect immunoprecipitation and analyzed by sodium dodecyl sulfate (SDS) polyacrylamide gel electrophoresis are composed of two subunits, the α and β polypeptides, with molecular weights of 33,000 and 28,000, respectively. Partial amino acid sequence data from the N terminus of Ia polypeptides isolated from lymphoid cells indicate that they apparently share little homology with either the K or D antigens or with immunoglobulins (Silver *et al.* 1976; McMillan *et al.* 1977).

The Ia antigens are more restricted in tissue distribution than the serologically detectable H-2K or D antigens. Whereas the K or D antigens are believed to be present on virtually every tissue, the Ia antigens have been detected only on B lymphocytes, a subpopulation of T lymphocytes, macrophages, fetal liver, epidermal cells, and spermatozoa. They are not present on red cells, platelets, muscle, brain,

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and a variety of other tissues (Hämmerling *et al.* 1975, Colombani *et al.* 1976, Hauptfeld *et al.* 1974).

The function of Ia antigens has been the subject of much speculation. They have been suggested as Fc receptors (Dickler and Sachs 1974), antigen receptors (Benacerraf and McDevitt 1972), T-B cell interaction molecules (Katz *et al.* 1975), and as a component of various inhibitory or facilitating immune factors (Tada *et al.* 1976, Munro and Taussig 1975). An unanswered question that may place important constraints on the function of Ia molecules is whether the Ia molecules on different tissues are identical.

Earlier studies using antisera produced against antigens determined by genes in the entire *I* region on spleen cells have demonstrated, by direct cytotoxic tests and by adsorption analysis, that Ia antigens are present on epidermal cells (Hämmerling *et al.* 1975, Klein *et al.* 1976). Preliminary evidence indicated that some Ia-like molecules could be precipitated from a radiolabeled epidermal cell extract by indirect immunoprecipitation (Delovitch and McDevitt 1975). Our present work demonstrates that the epidermal cells express Ia antigens encoded by genes in both the *I-A* and *I-EC* subregions. Moreover, antisera directed against either of these subregions precipitate two biosynthetically labeled Ia polypeptides, the molecular weights of which are indistinguishable from those present on B lymphocytes.

Materials and Methods

Mice. B10.A(4R), B10.HTT, and B10.D2 mice were raised at the mouse colony at the University of Southern California School of Medicine. B10.A(5R) mice were the generous gift of Dr. J. Stimpfling of McLaughlin Research Institute, Great Falls, Montana. C57B1/6J mice were purchased from the Jackson Laboratory, Bar Harbor, Maine.

Antisera. Hyperimmune alloantisera were prepared by multiple injections of spleen, lymph node, and thymus cells as previously described (David *et al.* 1973). All alloantisera have been characterized by direct cytotoxicity and adsorption analysis, using appropriate lymphocyte targets (Frelinger *et al.* 1974). The alloantisera employed in this study and the subregions they recognize on specific targets are given in Table 1. None of the antisera utilized recognizes *I-E* or *I-C* subregion products alone, so we denote this ambiguity as *I-EC*. Rabbit anti-μ chain serum was prepared from μ chains isolated from BALB/c myeloma tumor MOPC 104E, which was the generous gift of M. Kehry, California Insitute of Technology.

Adsorption of Anti-Ia Sera by Epidermal Cells. Epidermal cell suspensions were prepared as described below. Seventy-five μl undiluted antiserum were added to a cell pellet containing 5×10^6 epidermal cells. The cells were resuspended in the serum and incubated 30 minutes on ice. The suspensions were centrifuged and the supernatant was removed. This procedure was repeated 3 times. The final supernatant was tested for residual cytotoxic activity.

Staphylococcus aureus. Cowan-I strain ATC no. 12598 (Staph-A) was prepared according to the methods described previously (Kessler 1975) as modified by Cullen and Schwartz 1976). Briefly, *Staphylococcus aureus* Cowan I (Staph A) was grown overnight in shaker flasks, washed, heat-killed, and fixed with 1.5% formaldehyde. The fixed, heat-killed Staph A was stored in aliquots at −60°C until use. The staph A is superior to rabbit anti-mouse immunoglobulin as the agent for the indirect immunoprecipitation procedure with regard to ease of handling, efficiency, and specificity (Cullen and Schwartz 1976).

Preparation and Labelling of Cells. Spleen cells were labeled as described previously (McMillan *et al.* 1977). Briefly, cells were teased through a wire screen, washed, and incubated at 2×10^7 cells/ml for 5

Table 1. The Antisera and Mouse Strains Used as Targets to Precipitate Ia Molecules

Antisera	Targets	Relevant *H-2* Regions
A.TH anti-A.TL	B10.HTT[a]	$I\text{–}E^k$, $I\text{–}C^k$
	B10.D2[b]	$I\text{–}J^d$, $I\text{–}E^d$, $I\text{–}C^d$
	A.AL	I^k
A.TL anti-A.TH	B10.HTT[c]	$I\text{–}A^s$, $I\text{–}B^s$, $I\text{–}J^s$
(A.TH × B10.HTT)F_1 anti-A.TL	B10.A(4R)	$I\text{–}A^k$
(B10 × HTI)F_1 anti-B10.A(5R)	B10.D2	$I\text{–}E^d$, $I\text{–}C^d$
(A × B10.D2)F_1 anti-B10.A(5R)	C57B1/6J	K^b, $I\text{–}A^b$, $I\text{–}B^b$

[a] Since Ia-like membrane antigens have not been demonstrated for the *S* or *G* regions in lymphocytes, this antiserum is probably reacting principally with *I*-region molecules

[b] This antiserum potentially has reactivity with Ia.15 on B10.D2 cells. However, absorption with B10.HTT cells (Ia.7) leaves no residual activity on B10.D2 cells. Thus, this sera reacts primarily with Ia.7 and the molecule(s) precipitated is probably an *I–C* subregion product. Although crossreactions of $I\text{–}J^k$ and $I\text{–}J^d$ have been reported (Frelinger *et al.* 1976), *I–J* is expressed on only a small subpopulation of lymphocytes and probably does not contribute to the observed reactions

[c] Since no Ia specificities can be attributed to the *I–B* subregion and little compelling evidence can be produced for its existence, we have designated all reactions with *I–A* and *I–B*, *I–A*

hours in Hanks' balanced salt solution supplemented with 10 mM Hepes, Eagle's minimal essential media amino acids (minus tyrosine and leucine), 5% dialyzed calf serum, and 1 mCi each of ^{3}H-tyrosine and ^{3}H-leucine. T cells were isolated as described previously (Julius *et al.* 1973) and labeled as described above for spleen cells. Epidermal cells were prepared, using published procedures (Scheid *et al.* 1972), from mouse tails. Every cell preparation was examined microscopically, and each showed a morphology typical of epidermal cells. Cells were typically 2 or 3 lymphocyte diameters with prominent cytoplasm, and thus are easily distinguished from lymphocytes. Preparations were free of lymphocyte contamination. No small round cells were seen in several hundred epidermal cells observed. Only occasional red cells were seen, indicating little or no contamination of the epidermal cells preparations by peripheral blood cells. Mice with tail scars or lesions were excluded as cell donors. Epidermal cells were labeled as described above for spleen cells, but at a concentration of 1×10^7 cells/ml. Spleen or T-cell preparations were lysed in a volume equal to the incubation mixture, with 0.01 M Tris, 0.15 M NaCl, and 0.5% NP-40 at pH 7.4. Epidermal cells were lysed with the same buffer but at a concentration of 3×10^6 cells/ml lysis buffer. The debris was removed by centrifugation.

Lens culinaris Affinity Chromatography. Lens culinaris lectin was isolated from the common lentil (Hayman and Crumpton 1972) and coupled to CNBr-activated Sepharose 4B (Cuatrecasas *et al.* 1968) at 1.5 mg lectin/ml of settled Sepharose 4B. Nonidet (Shell trademark) P40 (NP-40) extracts were passed over a 10-ml lectin column at 4°C, and the bound fraction was eluted with 0.1 M alpha-methyl-D-mannoside. This fraction was concentrated to the original volume in a B15 Minicon filter (Amicon). This concentrated material was used in subsequent precipitations.

Immunoprecipitations. The lectin-purified extract was incubated with antisera, typically 400 μl NP-40 extract and 20 μl of a specific alloantisera, for 2 hours, and subsequently precipitated with Staph A for 1 hour, usually 200 μl 10% Staph A solution. The Staph A was washed 3 times and the bound material eluted with a mixture of 2% SDS, 2% 2-mercaptoethanol, and 50 mM Tris pH 6.8. This sample was examined by SDS-polyacrylamide gel electrophoresis (SDS-PAGE; Laemmli 1970). The gels were sliced into 1-mm sections, and the radioactivity was eluted and then counted in a Beckman LS230 scintillation counter.

Results

Ia Molecules Encoded by Genes in Both the I-A and I-EC Subregions Can Be Isolated from Epidermal Cells

Figure 1 shows the SDS-polyacrylamide gel analysis of labeled immunoprecipitates, employing a variety of antisera with restricted specificities (Table 1). Ia molecules encoded by genes in the $I\text{-}A^s$ (Fig. 1a), $I\text{-}A^k$ (Fig. 1b), and $I\text{-}A^b$ (Fig. 1c) subregions were isolated and characterized on SDS-polyacrylamide gels. Ia molecules from the $I\text{-}EC^k$ (Fig. 1d) and $I\text{-}EC^d$ (Fig. 1e) subregions were characterized in a similar manner. The sera and strains utilized as targets are given in the legend to Figure 1. The $H\text{-}2^{i5}$ and $H\text{-}2^d$ haplotypes share the Ia.7 specificity, and this is the cause of the reaction of (B10 × HTI)F_1 anti-B10.A(5R) with the B10.D2 extract (David *et al.* 1975; Fig. 1e). The peaks from the B10.D2 extract are substantially larger because a larger amount of cell extract was utilized for that precipitation relative to the other precipitation seen in Figure 1.

The Ia molecules encoded by genes in the *I-A* or *I-EC* subregions isolated from lymphocytes or epidermal cells are similar, if not identical, in their electrophoretic

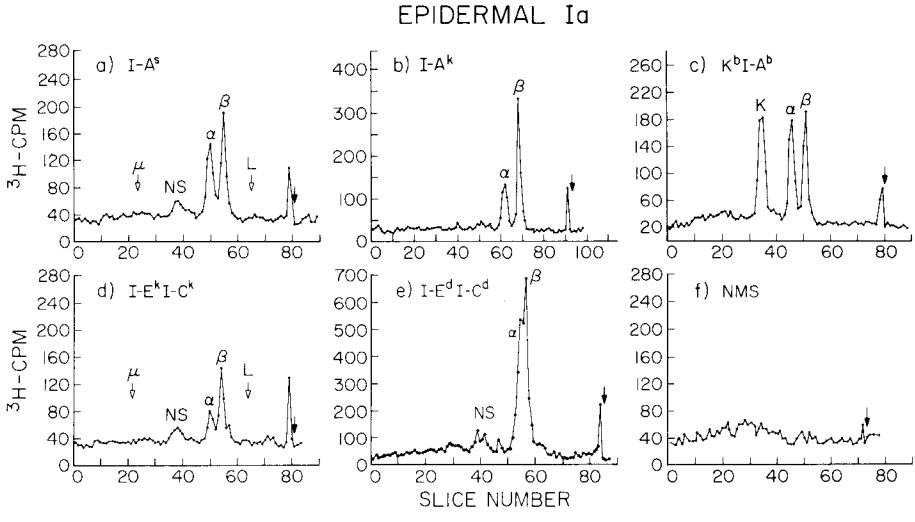

Fig. 1a–f. SDS-polyacrylamide gel electrophoresis patterns of Ia molecules isolated from epidermal cells by immunoprecipitation. Restricted Ia antisera and Staph A were used to precipitate Ia molecules from lectin-purified epidermal cell extracts. **a)** $I\text{-}A^s$ molecules detected by A.TL anti-A.TH on a B10.HTT extract representing 1.3 × 10^6 cells. **b)** $I\text{-}A^k$ molecules detected by (A.TH × B10.HTT)F_1 anti-A.TL on a B10.A(4R) extract representing 3 × 10^6 cells. **c)** K^b $I\text{-}A^b$ molecules detected by (A × B10.D2)F_1 anti-B10.A(5R) on a B10.A(5R) extract representing 1.3 × 10^6 cells. **d)** $I\text{-}E^k$ $I\text{-}C^k$ molecules detected by A.TH anti-A.TL on a B10.HTT extract representing 1.3 × 10^6 cells. **e)** $I\text{-}E^d$ $I\text{-}C^d$ molecules detected by (B10 × HTI)F_1 anti-B10.A(5R) on a B10.D2 extract representing 7.5 × 10^6 cells. **f)** Control employing normal mouse serum on a B10.A(5R) extract representing 1.3 × 10^6 cells. (⇨) Arrows indicate MOPC 104E heavy-chain (μ) and light-chain markers. (➡) Arrows indicate the dye front. NS represents the nonspecific peaks. All the extracts were precipitated by Staph A with the exception of the B10.D2 extract, which was preprecipitated with rabbit anti-μ chain antiserum and Staph A

behavior. Two molecular-weight components were resolved by this gel procedure in every case examined, though in general, the *I-EC* subregion components migrate with more similar Rf values than the components encoded in the *I-A* subregion. This is precisely the pattern seen in the Ia molecules isolated from spleen cells (Fig. 2). The molecular weights of splenic and epidermal Ia on SDS-polyacrylamide gels are identical within experimental error (±1000).

Epidermal Cells Remove Activity of Anti-Ia Serum

A.TH anti-A.TL (anti-I^k) serum was adsorbed with B10.S and A.TL epidermal cells. Adsorption of this serum with A.TL epidermal cells reduced the cytotoxic titer

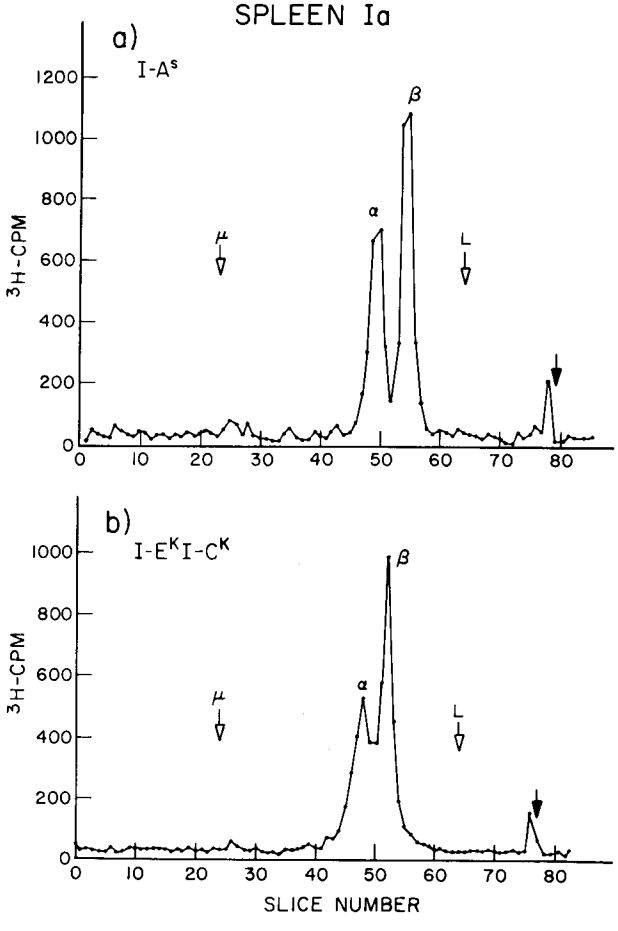

Fig. 2a and b. SDS-polyacrylamide gel electrophoresis patterns of Ia molecules from spleen. Lectin-purified B10.HTT spleen cell extracts representing 1 × 10^6 cells were precipitated with **a)** A.TL anti-A.TH, detecting *I-A^s* molecules, and **b)** A.TH anti-A.TL, detecting *I-E^k I-C^k* molecules. See the legend to Figure 1 for a description of the various markers

on lymph node lymphocytes from greater than 1/640 to less than 1/20. Adsorption with B10.S epidermal cells left a residual titer of greater than 1/320. Thus, A.TL epidermal cells share all the serological specificities present on A.TL lymph nodes cells detected by cytotoxicity.

Transplantation Antigens Can Be Isolated from Epidermal Cells

The peak of molecular weight 45,000 in Figure 1C is expected, because the antiserum used reacts with the K^b molecules. Thus, we have also shown that the serologically detectable K transplantation antigen is present on epidermal cells. The irregular peak of 45,000 molecular weight seen in some of the other extracts could be decreased in size by preclearing with Staph A, but was never completely eliminated. This peak probably represents nonspecific precipitation of actin (P. Jones, personal communication). We can eliminate this nonspecific peak by using the same procedure on spleen cell extracts (Fig. 2).

Epidermal Ia Molecules Are Not Contributed by B Cells (Ig-Positive Cells)

B10.D2 epidermal cells from mouse tails were isolated in the standard manner. This preparation was divided into two equal aliquots, one of which was labeled as described in *Materials and Methods*. C57B1/6J (B6) spleen lymphocytes were added

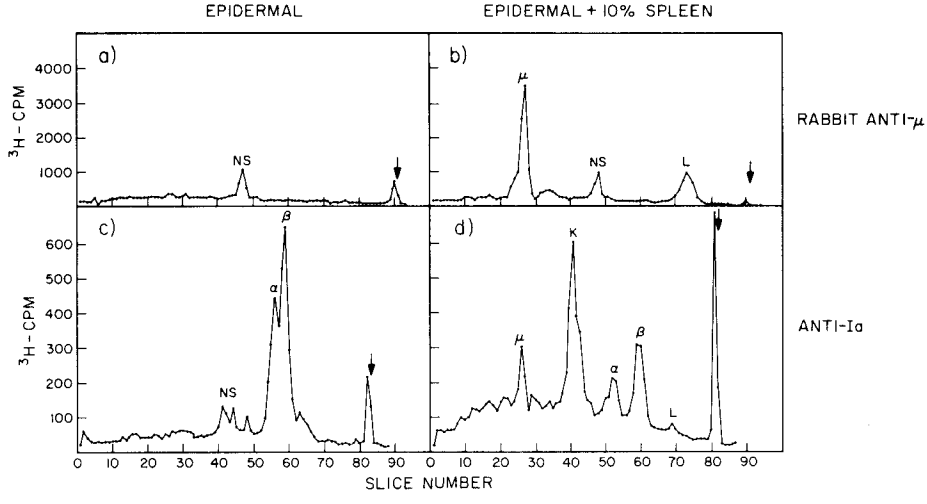

Fig. 3a–d. Mixture experiments with B cells and epidermal cells. **a)** SDS-polyacrylamide gel electrophoresis patterns of a lectin-purified B10.D2 epidermal cell extract representing 1.5×10^7 cells precipitated with rabbit anti-μ serum. **b)** Lectin-purified extract representing 1.5×10^7 B10.D2 epidermal cells and 1.5×10^6 B6 spleen cells, precipitated with rabbit anti-μ serum. **c)** One-half of the supernatant after the precipitation in (**a**) representing 7.5×10^6 B10.D2 epidermal cells precipitated with A.TH anti-A.TL serum. **d)** One-half of the supernatant after the precipitation in (**b**) representing 7.5×10^6 B10.D2 epidermal cells and 7.5×10^5 B6 spleen cells precipitated with (A × B10.D2)F_1 anti-B10.A(5R) serum. NS represents the nonspecific peaks. (➡) Arrows indicate the dye front

to the second aliquot to a concentration of ten percent of the epidermal cell number, and then labeled as the first aliquot. Both preparations were precipitated with rabbit anti-μ heavy chain. The analyses of these precipitations are shown in Figures 3a and 3b. One-half of the supernatant aliquot of B10.D2 tail cells was then precipitated with A.TH anti-A.TL (Fig. 3c). One-half of the supernatant from the aliquot of B10.D2 tails contaminated with B6 spleen cells was precipitated with (A × B10.D2)F_1 anti-B10.A(5R) (Fig. 3d). This serum recognizes only the Ia antigen from the spleen cells, since the antisera was made in an (A × B10.D2)F_1 mouse, and thus, is genetically blocked for reactivity with the B10.D2 Ia components present on the epidermal cells. The analysis of precipitates by SDS-polyacrylamide gel electrophoresis is shown in Figures 3c and 3d. No heavy-chain or light-chain peak is seen from twice the amount of extract necessary to observe an Ia peak from the B10.D2 tails alone, as can be seen by comparing Figures 3a and 3c. Furthermore, the heavy-chain peak seen in the artificially contaminated tail cells preparation is substantially larger (~fourfold) than the Ia peaks contributed by the spleen cells (Figs. 3b and 3d). If the Ia molecules in Figure 3c are from Ig-positive cells, we should be able to see easily a heavy-chain peak in Figure 3a, but this is not observed. Thus, contamination from B cells (Ig-positive) is not the source of the Ia antigen detected from the epidermal cell preparations. This finding is consistent with the absence of any fluorescent cells (0/40) when the epidermal cells were treated with fluorescein-labeled rabbit anti-mouse Ig (J.A. Frelinger, unpublished data).

T Cells Are Probably Not the Source of the Ia Molecules Seen in These Experiments

T cells were enriched by a passage of spleen cells through a nylon wool column (Julius *et al.* 1973). The labeled extract of the partially purified T cells was precipitated with both rabbit anti-μ chain and A.TH anti-A.TL. The results are shown in Figures 4a and 4b, respectively. The Ia present in Figure 4b could be explained by the presence of contaminating B cells, as evidenced by the amount of heavy chain and light chain in Figure 4a. The ratio of immunoglobulin to Ia molecules in the T-cell preparation is the same as that found in B or spleen cell preparations. This does

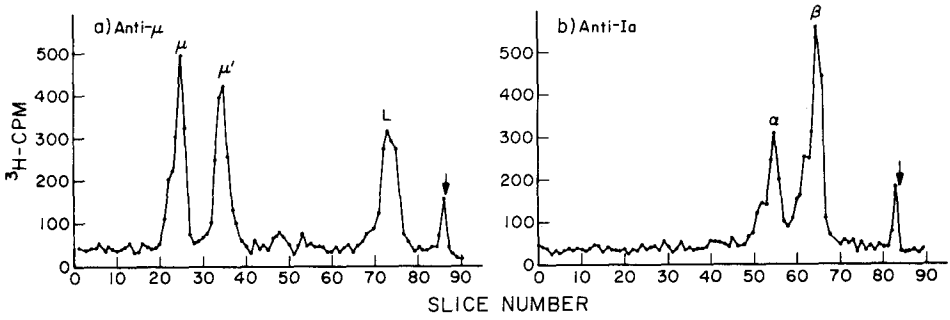

Fig. 4a and b. SDS-polyacrylamide gel electrophoresis patterns of immunoprecipitations from lectin-purified A.AL nylon wool T cell extracts representing 2 × 10^6 cells. **a)** T cells precipitated with rabbit anti-104E serum. **b)** T-cell extract precipitated with A.TH anti-A.TL serum. The μ' peak in Figure 4a probably represents a degradation product of the μ chain. (➡) Arrows indicate the dye front

not suggest that T cells lack Ia molecules. Others have estimated, using analogous techniques, that thymocytes have from 50 to 100 times less Ia per cell than B cells (Schwartz *et al.* 1977). However, within experimental limits, the amount of Ia precipitated in Figure 4b could be explained by the ten percent contaminating B cell estimated by direct immunofluorescence in this T-cell preparation. No Ia molecules could be ascribed to T cells in a cell preparation specifically enriched for T cells. We can rule out contamination of the epidermal preparations by more than five percent lymphocytes by morphological criteria. Thus, T cells are not a likely source of the Ia antigens seen in these epidermal cell extracts.

Discussion

Epidermal Ia Molecules Coded by Genes in the I-A and I-EC Subregions are Very Similar to Their Lymphoid Counterparts

Two Ia polypeptides can be isolated from the *I-A* and *I-EC* subregions from epidermal and spleen cell suspensions, using antisera prepared against lymphocytes. Thus, the epidermal and lymphoid Ia molecules share serological determinants. Further, the Ia molecules from epidermal and spleen cells share the charactertistic two-chain polypeptide pattern on SDS-polyacrylamide gels. The molecular weights of the Ia polypeptides isolated from spleen and epidermal cells are apparently identical. In addition, the size and shape of the subunit peaks from the two cell types are similar, when labeled with ^{3}H-tyrosine and ^{3}H-leucine, suggestive, although not definite proof, that the polypeptides have similar amino acid compositions. Finally, the Ia molecules from the *I-EC* subregion consistently migrate closer together than the molecules from the *I-A* subregion from both spleen and epidermal cells (Figs. 1 and 2).

Which Cells in the Epidermal Cell Preparation Are Responsible for the Synthesis of the Ia Molecules Seen in Our Experiments?

Tail cells were isolated by a procedure which characterized these cells as epidermal by their morphology in the electron microscope (Scheid *et al.* 1972). The Ia antigens are not derived from T or B cells (Figs. 3 and 4). However, our experiments give no direct information about either the proportion or the type of cells in the epidermis that are Ia-positive. Two previous reports of the expression of *I*-region markers on murine epidermal cells suggest that significant amounts of Ia are present on most epidermal cells. These studies employed direct cytotoxic tests to demonstrate that more than 80 percent of mouse epidermal cells have cell-surface Ia antigens which lead to cell lysis by anti-Ia sera and complement (Hämmerling *et al.* 1975, Klein *et al.* 1976). Indirect immunofluorescence studies suggest that more than 90 percent of cells in the epidermal cell suspensions are Ia-positive (J.A. Frelinger, unpublished data). Quantitative adsorptions suggest that epidermal cells have only two to four times fewer Ia molecules per cell than B cells (Klein *et al.* 1976). Unless one postulates cells with significantly greater amounts of Ia antigens than B cells, this adsorption data is not consistent with a small population of Ia-positive cells in the epidermis. Thus, the evidence in mice strongly suggests that most of the cells in the epidermis are Ia-positive.

The percentage of Ia-positive cells in human epidermis may be much lower than in mouse epidermis. Recent studies investigated which cells, keratinocytes, melanocytes, or Langerhans cells in the human epidermis are Ia-positive. Indirect immunofluorescence indicates only two to three percent of the cells in the epidermis, the macrophage-like Langerhans cells, are HLA-D-positive (Rowden and Sullivan 1977, Klaresky *et al.* 1977). The HLA-D region appears to encode the human equivalent of the Ia antigens. The reason for the apparent discrepancy in the frequency of Ia-positive cells in the epidermis of mouse and human is not clear. It might represent a species-associated difference in the distribution of Ia antigens. Alternatively, we believe that it probably reflects technical differences in the experimental system, such as differences in the titer of the antisera employed and the sensitivity of the detection system.

The Apparent Identity of Ia on Epidermal and B Cells Has Interesting Implications for the Function of Ia Molecules

There is no evidence which suggests any function for Ia molecules on epidermal cells, either immunological or other. Fluorescence studies in the human indicate that epidermal Langerhans cells are Ia-positive (Rowden and Sullivan 1977, Klaresky *et al.* 1977) and Fc-positive (Stingl *et al.* 1977, Rowden and Sullivan 1977). Other studies on guinea pigs show that Langerhans cells have an affinity for certain antigenic metals and amines (Shelly and Juhlin 1976). Furthermore, there is an increased number of Langerhans cells in the draining lymph nodes relative to controls in passively sensitized guinea pigs when they are rechallenged with antigen (Silberberg-Sinakin *et al.* 1976). Thus, investigators have suggested that Langerhans cells may function in a fashion analogous to macrophages and be involved in the uptake and transport of antigenic material from the epidermis to the lymphatic system. However, Langerhans cells probably represent only a subset of the Ia-positive cells in the mouse epidermis, which raises the question as to the function of the remaining Ia-positive cells. An interesting speculation is that the Ia molecules on skin cells are present to facilitate the stimulation of T cells associated with cells present in the epidermis. This hypothesis is consistent with the finding that the transfer of delayed-type hypersensitivity in mice requires *I-A* region compatibility of responding T cells and sensitizing macrophages (Miller *et al.* 1976). Besides predicting that the Ia molecules on epidermal and B cells would be identical, this also suggests that other tissues continuously exposed to environmental immunogens, such as the epithelial surfaces of the gut and lungs, should be Ia-positive. An alternative hypothesis is that the Ia molecules on the epidermis may assist in an immune surveillance function of T cells, possibly by stabilizing interactions between T and epidermal cells. In any case, theories as to the function of Ia molecules must take into account the presence of epidermal Ia molecules that appear to be similar if not identical to their counterparts on lymphoid cells.

We have demonstrated by immunoprecipitation techniques the presence on epidermal cells of Ia molecules similar to those found on B cells from both the *I-A* and *I-EC* subregions. These immunoprecipitation data are consistent with the serological and skin graft rejection data which indicate that Ia molecules are present on epidermal cells (Hämmerling *et al.* 1975, Klein *et al.* 1976). This system will permit the first detailed analysis of nonlymphoid Ia molecules. We are in the process of peptide map analyses and two-dimensional gel electrophoresis studies to determine if the epidermal and lymphoid Ia are, in fact, identical.

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