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Ontogeny and characterization of Factor XIIIa$^+$ cells in developing human skin

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Abstract Factor XIIIa (FXIIIa), a coagulation transglutaminase, is a cytoplasmic marker for dermal dendritic cells reported to be bone marrow-derived, phagocytic and antigen-presenting. In non-inflamed skin, these cells populate the papillary dermis in a perivascular distribution. They are increased in dermatoproliferative disorders and have been implicated as dermal stimulants for psoriatic hyperkeratosis. Since developing skin provides an example of dermal influence on the epidermis, we evaluated the presence of FXIIIa$^+$ cells in human fetal skin to determine whether their location would suggest a role in morphogenetic events in the skin. Embryonic and fetal skin of progressive estimated gestational ages (EGA) was examined using immunocytochemistry with a polyclonal antibody to FXIIIa. At 6 weeks EGA, globular FXIIIa$^+$ cells were present in the hypodermis. By 7–8 weeks, a compact sub-epidermal network of fusiform FXIIIa$^+$ cells was also evident. By 11–12 weeks, the sub-epidermal cellular network was no longer FXIIIa$^+$, but discrete FXIIIa$^+$ dendritic cells were present in the reticular dermis. With advancing gestational age, FXIIIa$^+$ dendritic cells populated the papillary dermis in a perivascular distribution. This adult-like distribution persisted through 22 weeks EGA, the oldest specimen examined. Because FXIIIa$^+$ cells were evident in embryonic skin before the onset of bone marrow hematopoietic function, the skin was double-labeled with the FXIIIa antibody and with monoclonal antibodies to CD45 (marker for bone marrow-derived cells), CD68 (marker for macrophages) and HLA-DR (class II major histocompatibility antigen). Most of the FXIIIa$^+$ dendritic cells did not colocalize CD45, but were CD68$^+$; some cells did react with the HLA-DR antibody. Notably, the FXIIIa$^+$ cells of the sub-epidermal network in the 7 weeks EGA specimens did not react with the other antibodies. We conclude that FXIIIa$^+$ cells are first present in embryonic hypodermis and sub-epidermal dermis and later they are distributed in the papillary dermis in a perivascular pattern. In embryonic skin FXIIIa$^+$ cells are not exclusively dendritic. Our data support the idea that cells that express FXIIIa do not constitute a unique bone marrow-derived cell type, but that multiple cell types produce FXIIIa.

Key words Fetal skin · Dermal dendrocyte · FXIIIa · CD45 · CD68

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Introduction

The dermal dendrocyte is a phagocyte characterized by the expression of the blood transglutaminase clotting protein factor XIIIa (FXIIIa) (Headington 1986; Cerio et al. 1989a, b; Cerio et al. 1990; Estrada and Piérard 1990). The cell resembles a fibroblast morphologically, but expresses markers characteristic of bone marrow-derived, antigen-presenting inflammatory cells (Cerio et al. 1989b; Sontheimer 1989; Sontheimer et al. 1989; Cerio et al. 1990; Estrada and Piérard 1990). In normal adult skin, the dermal dendrocyte is perivascular within the papillary and upper reticular dermis (Cerio et al. 1989b; Nickoloff and Griffiths 1989a, b; Sontheimer 1989; Sontheimer et al. 1989). Its presence in inflammatory dermatoses (e.g. psoriasis, eczema), Kaposi's sarcoma, dermatofibromas and acute burn wounds, but not in mature scars, keloids or fibroproliferative diseases (Nemes and Thomazy 1988; Cerio et al. 1988; Nickoloff and Griffiths 1989a, b; Nemeth and Penneys 1989; Cerio et al. 1989b; Toida et al. 1989; Penneys 1990; Cerio and Jones 1990a, b; Gray et al. 1990; Gray et al. 1991; Penneys et al. 1991; Regezi et al. 1993; Gibran et al. 1995a), suggests

that the dermal dendrocyte plays a role in the cellular phase of inflammatory processes.

It is distinct from the dendritic epidermal Langerhans cell by location, by negative reactivity with antibodies to CD1a (Headington 1986; Cerio et al. 1989b; Sontheimer et al. 1989) and by the absence of Birbeck granules (Moschella and Cropley 1990) and ATPase activity (Headington 1986). The dermal dendrocyte is considered to be bone marrow-derived, based on data that FXIIIa$^+$ dermal cells stain with antibodies to CD45, a surface marker for bone marrow-derived cells, CD11b, a leukocyte specific antigen, CD68, a macrophage marker (Headington 1986; Sontheimer 1989; Cerio et al. 1989b, 1990; Sontheimer et al. 1989; Estrada and Pérard 1990; Weber-Matthiesen and Sterry 1990). It is considered to be a phagocyte, based on the presence of vacuoles containing hemosiderin and melanin (Cerio et al. 1990) and is thought to be antigen-presenting as determined by positive labeling with antibodies to CD11b, CD14, CD36 and the class II major histocompatibility complex HLA-DR (Drijkoningen et al. 1987; Sontheimer 1989; Cerio et al. 1989b; Weber-Matthiesen and Sterry 1990). The immunophenotype of the dermal dendrocyte overlaps that of other antigen-presenting inflammatory cells in the skin and it may serve many of the same functions, but it is specifically identifiable because of its FXIIIa expression, dendritic appearance and dermal location. The literature is sufficiently controversial to make the identification of this cell equivocal. It may, in fact, be a unique phenotype of a common cell that can express CD1 under some conditions, contain Birbeck granules during periods of membrane endocytosis and express fibroblast markers at other times. Even the dendritic conformation may be dependent on the cell's attendant role and location.

Identification of the dermal dendrocyte in inflammatory conditions provides one perspective of the cell's potential role in the skin. Other aspects of morphogenesis, such as development, provide an opportunity to ask how the cell might relate to morphogenetic events that involve epidermal-mesenchymal interactions and whether it can arise from sources other than bone marrow such as the yolk sac or an uncommitted mesenchymal cell?

Embryonic and fetal human skin was evaluated for the immunolocalization of FXIIIa$^+$ dendritic cells. Further characterization of the FXIIIa$^+$ cells was pursued by examining the skin for other cell markers; because dermal dendrocytes are reputed to be bone marrow-derived, the tissue was also stained with antibodies to CD45, the marker for bone marrow-derived cells, and CD68, the marker for macrophages/monocytes. An antibody to the major histocompatibility antigen HLA-DR was used to examine antigen presenting capacities of the FXIIIa$^+$ cells.

Materials and methods

Human Skin

Thirty-six specimens of human fetal skin ranging from 6 to 22 weeks estimated gestational age (EGA) were examined for this study. Fetal age was determined by foot length and crown-rump length. The tissue was obtained through the Central Laboratory for Human Embryology in accordance with the regulations of the University of Washington Human Subjects Review Board and with DHEW policies. No identifying data for any of the patients were available to the investigators. The tissue was immersed in Carnoy's fixative overnight, dehydrated, paraffin-embedded and cut in 6 μm sections.

Immunocytochemistry

Initial studies with tissue frozen in OCT demonstrated that unfixed tissue stained with greater intensity but with no difference in distribution of positive cells. Also, trypsin treatment enhanced the FXIIIa staining, but did not change the distribution of positive cells. Therefore, Carnoy's fixed tissue without protease treatment was used for all the experiments. The immunocytochemistry was performed using a previously described immunoperoxidase technique (Gibran et al. 1994b). Deparaffinized sections were incubated with 3% H_2O_2 and incubated in 1% bovine serum albumin that was also used as a diluent for the polyclonal antibody to FXIIIa (1:1000; CalBiochem, Calif., USA). Biotinylated anti-rabbit IgG (1:300; Vector Laboratories, Calif., USA) was used followed by Streptavidin AH-biotin amplification (Zymed Laboratories, Calif., USA). All rinses were performed in 0.01 M TRIS saline pH 7.4. The chromagen was 0.1% 3',3'-diaminobenzidine (Sigma Chemical Co, Mo., USA), and hematoxylin was used as a nuclear counterstain. Control specimens without primary antibody were included in each immunochemical run. Slides were dehydrated and coverslipped using Histomount (National Diagnostics, N.J., USA). The slides were photographed using a Zeiss Standard microscope with planapochromatic lenses.

For double-immunolabeling experiments, a previously described immunofluorescent method was used (Gibran et al. 1995a). The sections were deparaffinized, incubated with the 1% BSA and incubated with monoclonal antibodies to CD-68 (1:400; Dakopatts Calif., USA), a marker for monocytes/macrophages; CD-45 (1:25; Dakopatts), a marker for bone marrow-derived cells; or HLA-DR (1:70, Dakopatts), the class II major histocompatibility antigen. Biotinylated anti-mouse IgG antibody (1:200; Vector Laboratories) was followed by incubation with rhodamine 600-avidin D (1:1500; Vector Laboratories). After TRIS saline rinses, the slides were again incubated with 1% BSA followed by the polyclonal antibody to FXIIIa (1:100) and finally fluorescein labeled anti-rabbit IgG antibody (1:40; Vector Laboratories). Control slides without primary antibody were included in these runs. Slides were coverslipped with Fluoromount-G (Southern Biotechnology Associated) and photographed within 48 h using a Zeiss Standard microscope and a Zeiss filter (excitation wavelengths 450–490).

Results

At 6 weeks EGA, globular FXIIIa$^+$ cells were present in the hypodermis, but FXIIIa$^+$ dendritic cells were not present in the dermis or epidermis. The FXIIIa$^+$ cells in the hypodermis were large and round, typical of a tissue macrophage (Fig. 1a). By 7–8 weeks EGA, a compact sub-epidermal network of fusiform FXIIIa$^+$ cells resembling fibroblasts was present in addition to the globular cells in the hypodermis (Fig. 1b). By 11–12 weeks, globular FXIIIa$^+$ cells still populated the hypodermis and dendritic FXIIIa$^+$ cells were present in the deep dermis, but the sub-epidermal network of compact mesenchymal cells was no longer FXIIIa$^+$ (Fig. 1c, d). The dendritic FXIIIa$^+$ cells were concentrated around capillaries in the

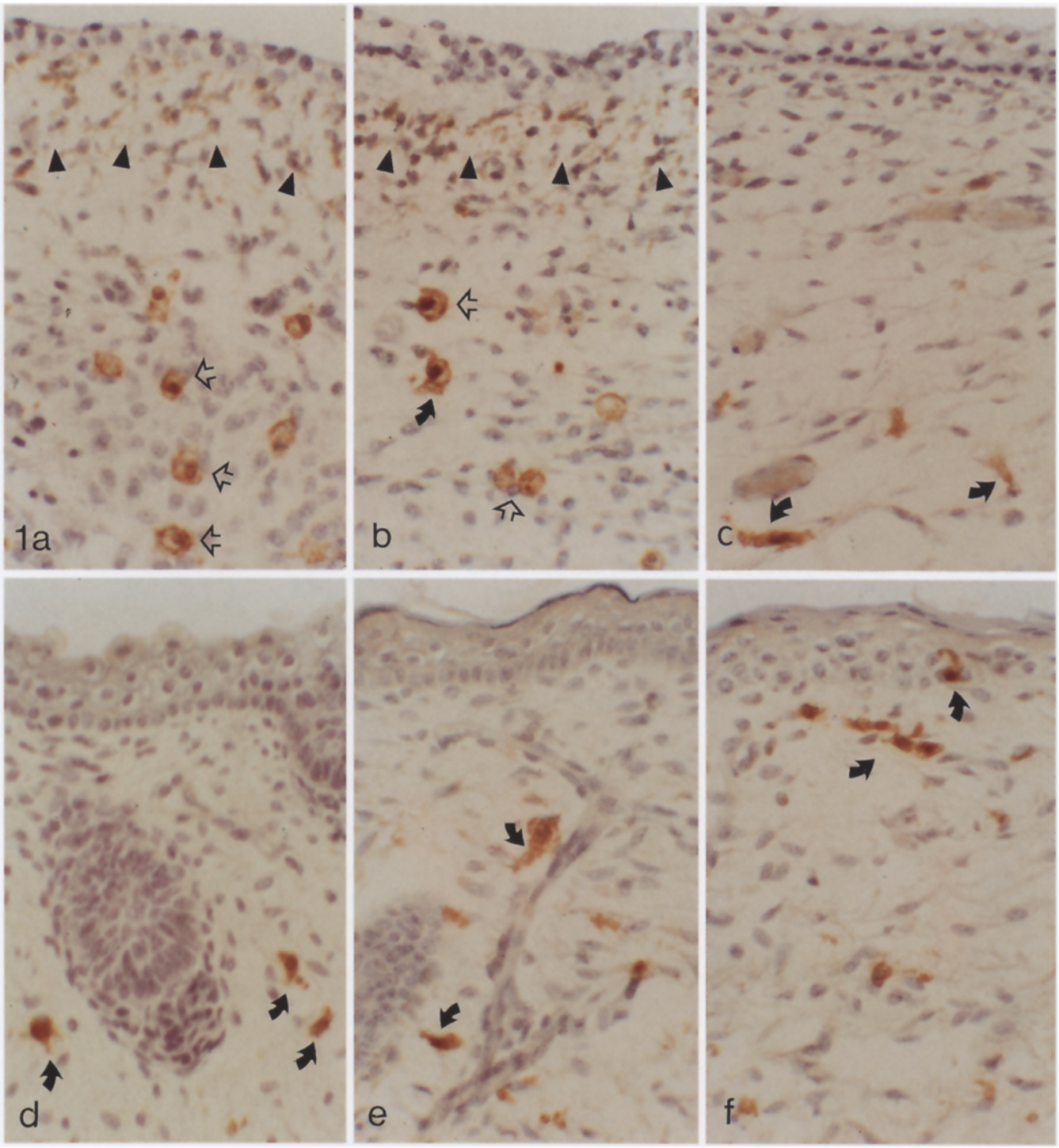

Fig. 1 Light micrographs from: **a** 6-week, **b** 7-week, **c** 11-week, **d** 14-week, **e** 21-week, **f** 22 week human embryos and fetuses immunolabeled with an antibody to factor XIII subunit a. Note the presence of FXIIIa$^+$ globular (*open arrows*) and dendritic (*curved arrows*) within the hypodermis as early as 6 weeks EGA (**a**). The band of sub-epidermal cells is evident in the early dermis, but is absent from older skin (**a, b** *arrowheads*). The perivascular cellular distribution is illustrated in **c, e** and the absence of an association with epidermal appendages is shown in **d**. The presence of FXIIIa$^+$ cells in the epidermis is evident in **f**. *Bar* 25 μm

papillary dermis in a distribution similar to that in adult skin (Fig. 1c). The papillary distribution of dendritic FXIIIa$^+$ cells persisted through our oldest (22 weeks) EGA specimen (Fig. 1e, f). With increasing gestational age, there was an apparent progression of FXIIIa$^+$ dendritic cells within the reticular dermis towards the papillary dermis and epidermis with a decrease in the number of globular FXIIIa$^+$ cells in the hypodermis. FXIIIa$^+$ cells did not appear to have specific relationships with developing epidermal appendages.

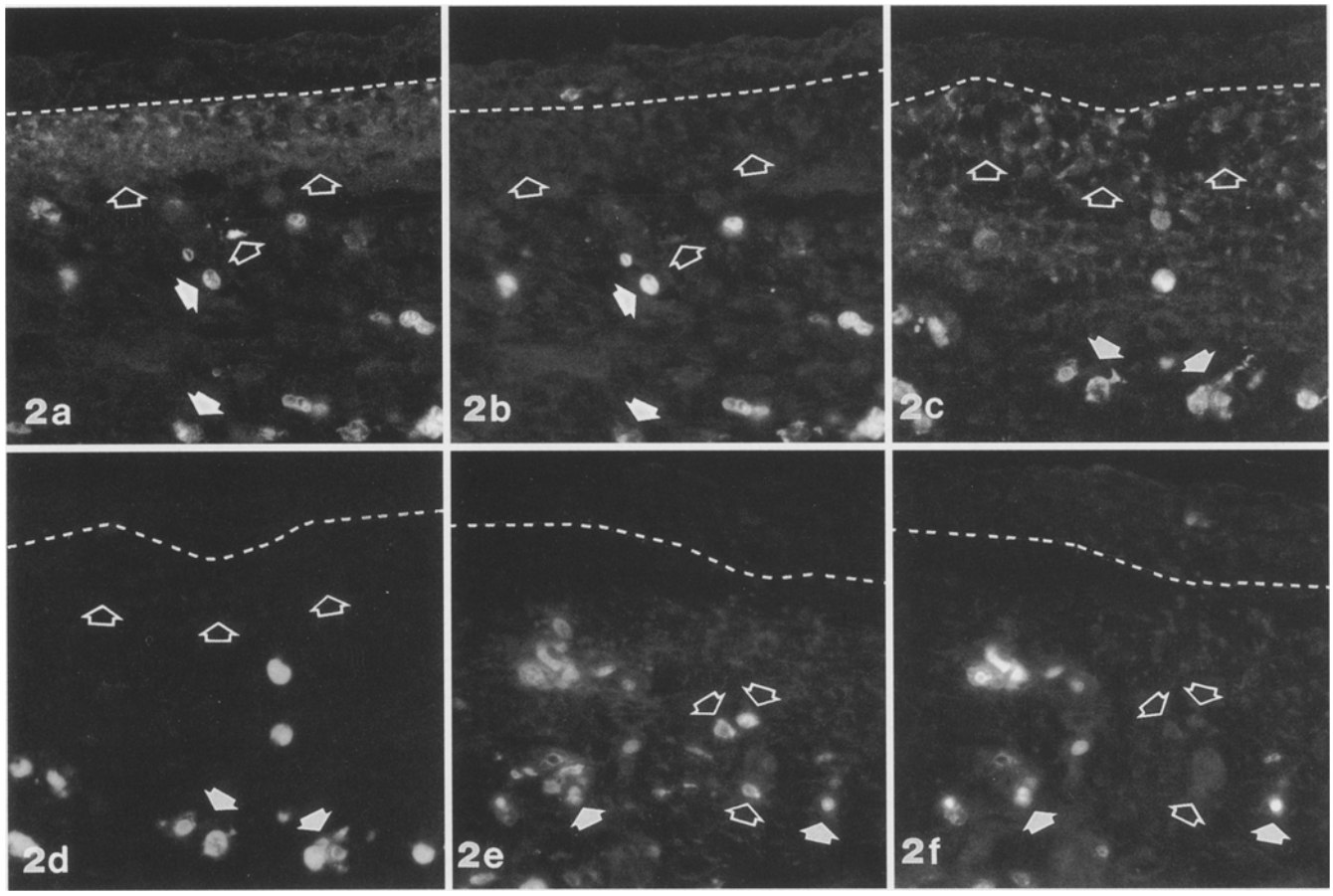

Fig. 2 Skin sections from a 7-week EGA embryo double-labeled with immunofluorescence using antibodies to: **a, c, e** factor XIIIa, **b** CD45, **d** CD68 or **f** HLA-DR. *Broken line* delineates the dermal-epidermal junction. *Open arrows* depict examples of cells that localize only FXIIIa. *Solid arrows* illustrate examples of cells that localize both cell markers. *Bar* 25 μm

Further characterization of these cells with double-labeling demonstrated variable co-localization of FXIIIa with CD45, CD68 and HLA-DR. The sub-epidermal network seen at 7–8 weeks did not immunostain with antibodies to CD68, CD45 or HLA-DR (Fig. 2a–f). Many FXIIIa$^+$ globular cells in the hypodermis were immunoreactive with the antibody to CD45, whereas many dendritic dermal FXIIIa$^+$ cells did not localize CD45. This pattern persisted through all of the gestational ages examined (Figs. 2a, b, 3a, b). Except for the FXIIIa$^+$ subepidermal cellular network, FXIIIa$^+$ cells routinely co-localized CD68 (Figs. 2c, d, 3c, d). HLA-DR localized to some but not all of the FXIIIa$^+$ cells in the dermis (Figs. 2e, f, 3e, f). Expression of HLA-DR did not correlate with the morphological shape of the cells.

Discussion

The potential sources and role of Factor XIIIa$^+$ cells have not been definitively determined. Data about the dermal dendrocyte's presence in different dermatopathologic states and conclusions about its presumptive role are often conflicting (Nemes and Thomazy 1988; Cerio et al. 1988; Nemeth and Penneys 1989; Nickoloff and Griffiths 1989a, b; Cerio et al. 1989b; Toida et al. 1989; Penneys 1990; Cerio and Jones 1990a, b; Gray et al. 1990, 1991; Penneys et al. 1991; Regezi et al. 1993; Gibran et al. 1994a). Distinction of the dermal dendrocyte from fibroblasts, macrophages, Langerhans cells and other dendritic cells of the immune system has been based on immunocytochemical localization of cell markers. There is no direct evidence that the dermal dendrocyte is a unique cell type. Rather, FXIIIa$^+$ cells may represent a phenotype of dermal mesenchymal cells that are sufficiently plastic to express different cell markers at specific stages of differentiation and/or the cell cycle and also to alter morphology based on the extracellular matrix and neighboring cells.

Our earliest embryonic tissue has large round FXIIIa$^+$ cells, resembling other tissue macrophages, in the hypodermis. However, FXIIIa$^+$ cells never appear globular in the papillary dermis in any embryonic or fetal skin specimens, suggesting that the hallmark spindle-shape morphology of the dermal dendrocyte may depend on location, extracellular matrix architecture or specific cellular interactions. Alternatively, FXIIIa may be expressed by several cell types, including fibroblasts and macrophages and each cell type may be able to express Factor XIIIa under specific, yet undefined, conditions.

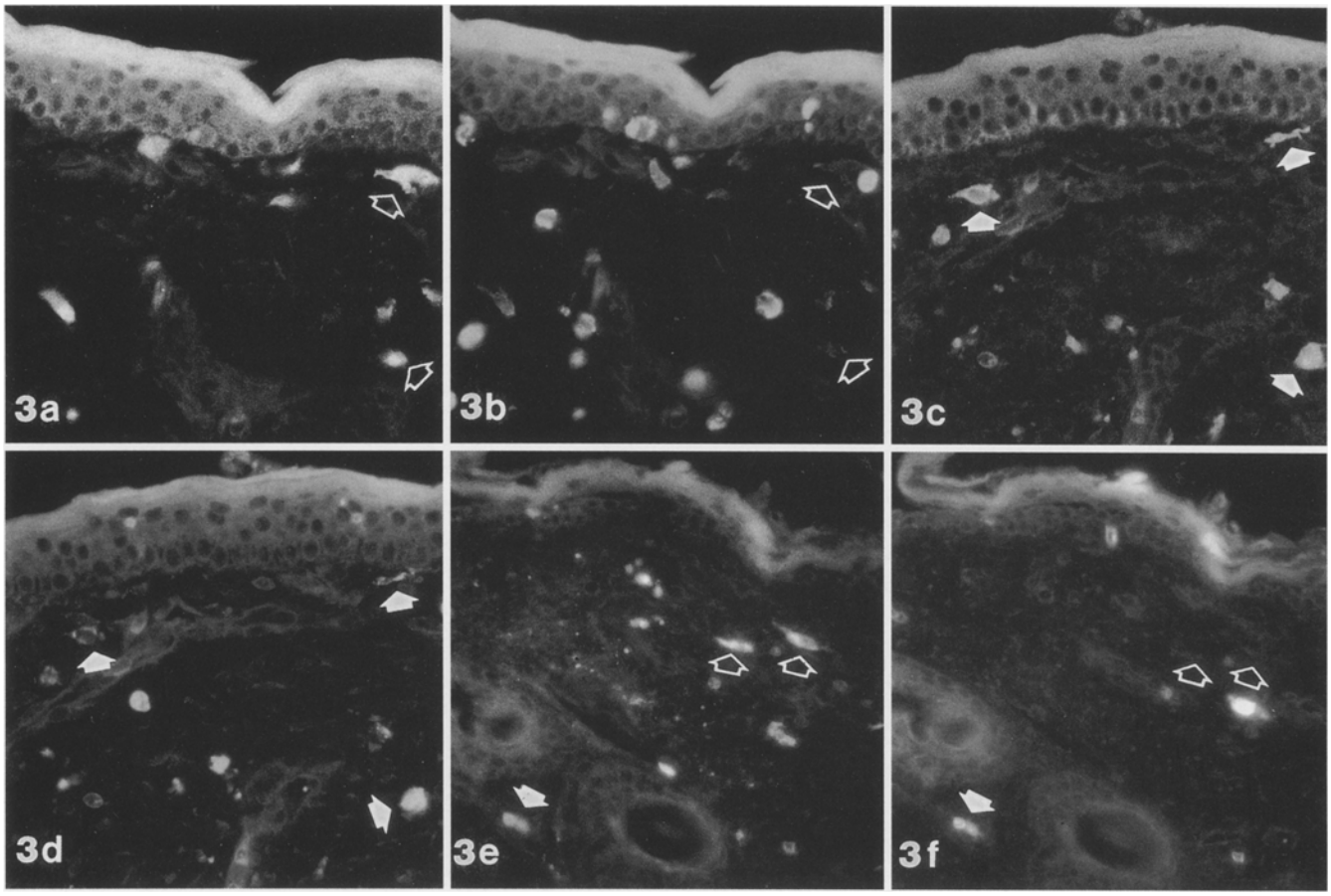

Fig. 3 Skin sections from a 22-week EGA fetus double-labeled with immunofluorescence using antibodies to: **a, c, e** factor XIIIa and either **b** CD45, **d** CD68 or **f** HLA-DR. *Open arrows* depict examples of cells that localize only FXIIIa. *Solid arrows* illustrate examples of cells that localize both cell markers. *Bar* 25 μm

Nickoloff has suggested that dermal dendrocytes increase their expression of TNFα in psoriatic lesions and has proposed that this induces an autocrine hyperproliferative response by the overlying keratinocytes (Nickoloff et al. 1991). Trimble and colleagues, in their investigation of FXIIIa$^+$ cells in developing human tissues, reported a sub-epidermal "cambium" of FXIIIa$^+$ cells in the skin (Trimble et al. 1992), but the authors did not report variation in this cellular localization with gestational age. Our data suggest that the sub-epidermal concentration of FXIIIa$^+$ cells is transient and is present at the stage when the epithelium stratifies from a two-cell-layered structure to a three-layered epidermis and thus may support the hypothesis that FXIIIa$^+$ dendritic cells influence epithelial cell proliferation. We did not observe a specific relationship between FXIIIa$^+$ cells and developing epidermal appendages at any gestational age that would suggest a relationship between FXIIIa$^+$ cells and epithelial morphogenesis. However, signaling between dermal FXIIIa$^+$ cells and epidermal cells during early gestation may contribute to the eventual development of epidermis-derived structures.

The first evidence of the perivascular localization of the FXIIIa$^+$ dendritic cells, a distribution that has been well described in adult skin, occurs at 10–11 weeks EGA, the period of transition between embryonic and fetal development, and coincident with the establishment of the subpapillary plexus (Johnson and Holbrook 1989). Our data suggest that the presence of FXIIIa$^+$ dendritic cells in the papillary dermis is not dependent on dermal vascularity alone, since the earlier embryonic specimens have dermal capillary networks but no papillary dermal FXIIIa$^+$ cells. Nevertheless, the vessel distribution in older fetal skin is more continuous than at younger gestational ages (Johnson and Holbrook 1989) and may allow greater cellular migration to the extracellular space. Wagner has proposed that endothelial and blood cells differentiate from a common mesenchymal stem cell that is derived from yolk sac blood islands (Wagner 1980). Therefore, our identification of FXIIIa$^+$ dermal dendritic cells at an embryonic stage, when the dermal vasculature is also developing, might relate to the common origins of endothelial cells and bone marrow-derived cells. This close relationship between the hematopoietic system and endothelial cells may also be illustrated by evidence that endothelial cells stimulated in vitro upregulate FXIIIa expression (Karasek 1991).

Although FXIIIa$^+$ cells have been reported to be bone marrow-derived (Headington 1986; Sontheimer 1989; Cerio et al. 1989b; Sontheimer et al. 1989; Estrada and

Piérard 1990; Weber-Matthiesen and Sterry 1990; Cerio et al. 1990), our data indicate that FXIIIa+ cells exist in the skin as early as 6–7 weeks EGA, prior to hematopoietic function by the bone marrow (Keleman and Calvo 1982). Moreover, FXIIIa+ dendritic cells in the fetal and embryonic dermis only sporadically localize CD45, the marker for bone marrow-derived cells. This suggests that non-bone-marrow-derived mesenchymal cells may transiently express FXIIIa or that uncommitted cells may differentiate to become FXIIIa+ dendritic cells. Co-localization of CD68, a surface marker for macrophages, on FXIIIa+ cells supports the hypothesis that the dermal dendrocyte belongs to an inflammatory cell lineage; therefore, the cells could derive from the yolk sac and settle in the dermis as tissue macrophages that undergo phenotypic change, including expression of FXIIIa, in response to appropriate stimuli. Eighty-five percent of non-stimulated FXIIIa+ cells have been reported to express the class II major histocompatibility antigen HLA-DR (Cerio et al. 1989b). Our observations of HLA-DR expression by embryonic and fetal FXIIIa+ cells correlate with published data and do not appear to vary with gestational age. Variable HLA-DR expression may indicate that not all FXIIIa+ cells are constitutively stimulated to present antigens. Alternatively FXIIIa+ cells may represent multiple cell types with common expression of a ubiquitous enzyme; some of the FXIIIa+ cells may be antigen-presenting cells and others may be non-inflammatory cells. Our data are supported by other recent reports of phenotypic and functional subsets of FXIIIa+ dermal cells. Expression of either the CD1a or CD14 antigen and the ability of the CD1a+ cells to induce T cell proliferation has been reported as a distinguished feature of different subsets of FXIIIa+ dermal cells (Nestle et al. 1993). Therefore, the variable expression of HLA-DR in our tissues is expected and may reflect different states of FXIIIa+ cells or may represent different cell types that are all capable of FXIIIa expression.

To conclude, we have demonstated that more than one population of FXIIIa+ cells may be present in embryonic and fetal skin. Our data suggest that the enzyme is present in a population of tissue macrophage-like cells in the hypodermis, a transient fusiform network of fibroblast-like cells in the sub-epidermal dermis and a perivascular dendritic population in the papillary dermis. Variable expression of inflammatory cell surface markers on the FXIIIa+ cells in embryonic and fetal specimens suggest that multiple phenotypes of FXIIIa+ cells exist or that multiple cell types have the potential to express FXIIIa. These results support the possibility that the bone marrow is not the only source for FXIIIa+ cells. We suggest that multiple cell types may express FXIIIa, similar to the expression of other transglutaminases by terminally differentiated cells (Jetten and Shirley 1986; Piacentini et al. 1991), rather than FXIIIa being a specific marker for a unique cell type.

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