

Factor XIIIa-Expressing Dermal Dendrocytes in AIDS-Associated Cutaneous Kaposi's Sarcomas

Kaposi's sarcoma (KS) is an angioproliferative neoplasm that develops as multifocal lesions, often involving the skin, accompanied by the accumulation of perivascular and interstitial spindle-shaped cells (1). The nature of the proliferating spindle-shaped cells in KS has been a "riddle within a puzzle" for the past century [reviewed in (2)]. While the endothelial cell has been linked to the spindle-shaped cells in KS lesions (3), two recent reports (4) suggest a nonvascular origin of the spindle-shaped cells in AIDS-associated KS lesions. Because the cultured cells derived from AIDS-associated KS lesions had morphological features including "dendritic" spindle cells (4), we asked whether these cells could be related to the dermal dendrocyte, a normal constituent of skin first described by Headington (5). The dermal dendrocyte is a member of the mononuclear phagocytic system (5) and shares with other monocytes/macrophages the expression of factor XIIIa antigen (6). Furthermore, both the dermal dendrocyte and cultured KS spindle-shaped cells possess the same enzymatic content, including acid phosphatase

and nonspecific esterase, while lacking adenosinetriphosphatase and factor VIII-related antigen; they also both have pinocytotic vesicles but no Birbeck granules (4, 5). To determine whether the spindle-shaped cell proliferation in AIDS-associated KS lesions included factor XIIIa antigen-expressing dermal dendrocytes, we analyzed 14 AIDS-associated cutaneous patch-and-plaque stage KS lesions obtained from 11 different patients.

The KS lesions were characterized by a complex histological picture, including numerous slit-like vascular spaces, perivascular spindle-shaped cells that stained positively for factor XIIIa, lymphocytes, and plasma cells (Fig. 1 and Fig. 2). In four of the AIDS-associated KS cases, the factor XIIIa-positive cells represented approximately 30 to 50% of the spindle-shaped cells within the lesions; in eight other cases they were between 10 and 30% of cells; in two cases they represented approximately 10% of the spindle-shaped cells. It appeared that in those cases in which there was a greater proportion of factor XIIIa-positive dermal

dendrocytes among the spindle-shaped cells, there was a greater degree of lymphocytic inflammation. The factor XIIIa staining pattern in all 14 KS lesions was heterogeneous; this heterogeneity is similar to the staining pattern of another cutaneous neoplasm that contains a significant accumulation of dermal dendrocytes known as the dermatofibroma (7). The dermatofibroma, which may be difficult to distinguish from KS lesions (8), also contains proliferating small vessels and spindle-shaped cells embedded in a collagenous stroma with admixed lymphocytes. The factor XIIIa-positive cells in KS lesions appeared as fascicles of spindle-shaped cells, or as individual dendritic-shaped cells inter-

Fig. 1 (top). HIV-1-associated KS with collections of factor XIIIa-positive red-stained spindle-shaped cells (straight arrows) in the dermis embedded in a collagenous stroma interspersed with numerous vascular spaces (curved arrows), extravasated erythrocytes, and interstitial lymphocytes. Magnification, $\times 200$. Sections (5 μ m thick) of paraffin-embedded skin were cut, dewaxed in xylene, and rehydrated. The sections to be stained for factor XIIIa were then incubated with trypsin in phosphate-buffered saline at 37°C for 30 min and endogenous peroxidase was blocked with 1% H₂O₂ in methanol for 20 min. An avidin-biotin peroxidase technique (Vectastain ABC Kit, Vector Labs. Inc.) with the polyclonal rabbit antibody to factor XIIIa (Calbiochem Corp., diluted 1:400) was used with 3-amino-9-ethylcarbazole as the chromogen, and the sections were counterstained with 1% hematoxylin. When either normal rabbit serum, or rabbit antibody to the plasma-derived, extracellular form, factor XIIIa was used (Calbiochem Corp.), there was no staining. **Fig. 2 (bottom).** HIV-1-associated cutaneous KS. Only perivascular spindle-shaped cells dissecting between collagen bundles, and not endothelial cells lining the vessels (asterisk), are factor XIIIa-positive, as defined by red cytoplasmic staining. This site of prominent factor XIIIa expression is accompanied by a relatively dense lymphocytic infiltrate. Magnification, $\times 250$.

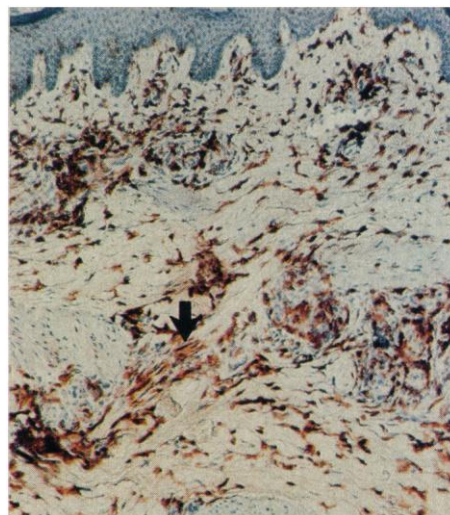
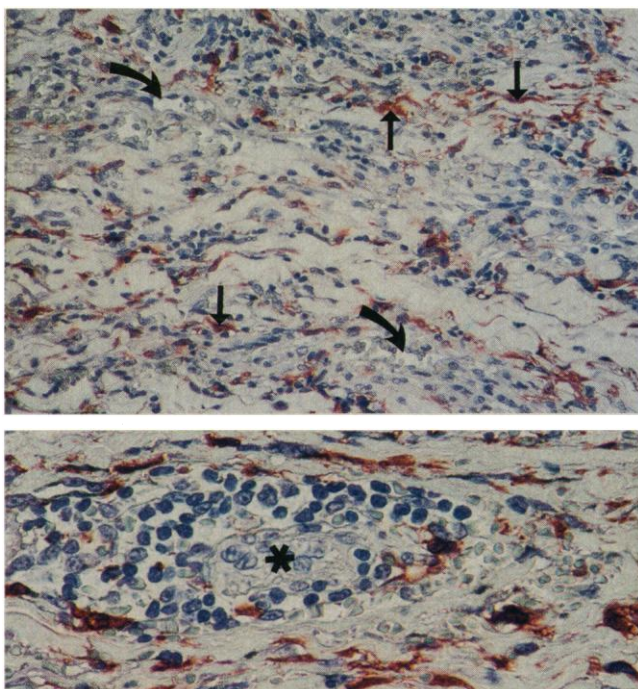


Fig. 3 (top). Many dermal dendrocytes in HIV-1-associated KS lesion are LFA-1-positive with focal formation of fascicles of spindle-shaped cells (arrow). Magnification, $\times 25$. Cryostat sections (6 μ m thick) were immunohistochemically stained with the use of anti-LFA-1 monoclonal antibody [TS 1.18 (10)], and the avidin-biotin peroxidase technique described above was used. **Fig. 4 (bottom).** HIV-1-associated psoriasis demonstrating numerous but solitary angiocentric factor XIIIa-positive dermal dendrocytes in papillary dermis immediately beneath hyperplastic epidermis. Magnification, $\times 100$.

spersed among dermal collagen bundles. The factor XIIIa-positive spindle-shaped cells were not S-100 positive, which rules out a Langerhans cell or a Schwann cell origin (9). As in normal skin, where factor XIIIa-positive dermal dendrocytes are closely associated with blood vessels, many factor XIIIa-positive spindle-shaped cells in the KS lesions maintained an angiocentric configuration. Occasional factor XIIIa-positive spindle-shaped cells also contained phagocytic hemosiderin deposits, which would be in agreement with the previously recognized ability of dermal dendrocytes to engulf pigments (5). In the last two AIDS-associated KS patients, the spindle-shaped cells were identified in cryostat sections as also staining with antibody to an antigen (LFA-1) that has been associated with lymphocyte function (Fig. 3), confirming that they were bone marrow-derived mononuclear cells and not fibroblasts or endothelial cells (11).

These results suggest that the factor XIIIa-expressing dermal dendrocyte may be the cell of origin for the spindle-shaped cell population in AIDS-associated KS lesions and in the KS cell line (4). Our results confirm an earlier suggestion (2) that the spindle-shaped cells in KS lesions are related to the reticuloendothelial cell system by demonstrating a monocyte/macrophage lineage marker (factor XIIIa) in the dermal dendrocytes that make up the spindle-shaped cell population. The cause of the variation in the extent of factor XIIIa expression by the spindle-shaped cells in AIDS-associated KS lesions is not known, but because there was a greater expression when there were more lymphocytes in the infiltrate, we believe that local modulation by interferon- γ may play a role (12). In one of our AIDS patients who developed psoriasis, a skin disease with prominent blood vessels and inflammation, we observed large numbers of factor XIIIa-positive dermal dendrocytes in the papillary dermis immediately

beneath the hyper epidermis (Fig. 4). These results suggest that upon exposure to human immunodeficiency virus type 1 (HIV-1), factor XIIIa-positive dermal dendrocytes may be activated that can give rise either to expansile lesions such as KS or to altered local immune reactions producing psoriasis in genetically susceptible individuals. In either case, it would appear that the cutaneous manifestations of HIV-1 infection such as KS and psoriasis may represent hyperactivity of the dermal dendrocytic component of the immune system, rather than an immunodeficiency (13). If factor XIIIa dermal dendrocytes in vivo possess the same repertoire of cytokine production (including interleukin-1 and basic fibroblast growth factor) as do the cultured KS spindle-shaped cells (4, 14), then it is possible to envisage the molecular basis by which HIV-1-activated dermal dendrocytes could stimulate endothelial, keratinocyte, and mononuclear cell proliferation in AIDS-associated KS and psoriatic lesions (15).

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Response: Nickoloff's comment is interesting. It could be that the true primary neoplastic cell of Kaposi's sarcoma (KS) is the spindle cell, as he suggests and as we and others believe. Nickoloff also argues that the long-sought-after origin of these cells may be the so-called dermal dendrocytes and suggests that the spindle cells we succeeded in culturing for the first time from KS patients may indeed be these cells. Indeed, many of the properties of our cells are similar to properties of macrophages. However, such cells are difficult to distinguish from endothelial cells. For instance, in terms of uptake of low density lipoprotein, binding of *Ulex europaeus* lectin, and presence of cytokeratin our cells are more like endothelial cells than macrophages. Of course, dermal dendrocytes may be in the macrophage lineage but different from classical macrophages in these respects. However, KS is not limited to the skin, but occurs in numerous other tissues. Thus, the suggestion seems far from conclusive, but it does merit testing our cultured KS cells with the antibodies to factor XIIIa and LFA-1. It will be critical to confirm the specificity of the antibody to LFA-1.

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