Oral submucosal dendrocytes: factor XIIIa$^+$ and CD34$^+$ dendritic cell populations in normal tissue and fibrovascular lesions

Factor XIIIa$^+$ and CD34$^+$ dendritic cells, believed to be subsets of monocyte/macrophages, have been identified in dermis and in dermal tumors. The purpose of this study was to determine the presence and distribution of analogous cell types in oral submucosa and oral fibro-vascular lesions. Antibodies to XIIIa, CD34, S-100 protein, and macrophage antigen (MAC 387) were tested on formalin-fixed, paraffin-embedded tissue sections from normal mucosa, peripheral fibroma (PF), peripheral ossifying fibroma (POF), peripheral giant cell granuloma (PGCG), pyogenic granuloma (PG), lymphangioma (La), benign fibrous histiocytoma (BFH), idiopathic histiocytosis (IH), angiofibroma (Af) using an ABC immunoperoxidase technigue. Numbers of positively stained cells were compared to unstained cells in the tumors. XIIIa positive submucosal dendrocytes (CD34-, S-100-, MAC 387-) were found in abundance in normal tissue in characteristic distributions: collagen-associated, vessel-associated, and lymphoid-associated. The percentage of XIIIa$^+$ cells in the oral tumors was as follows: PF: 10–30%, POF: 5–10%, PGCG: 0–5%, PG: 5–20%, La: 0%, BFH: 5–25%, IH: 0%, and Af: 10–20%. CD34$^+$ dendrocytes (XIIIa-, S-100-, MAC 387-) were few in number and were found in deeper submucosa, especially around skeletal muscle. Other than blood vascular endothelium, CD34$^+$ cells were not generally seen in the oral tumors studied. It is concluded that two previously unrecognized dendrocyte populations reside in normal submucosa. XIIIa$^+$ cells participate in the formation of some oral reactive and neoplastic lesions.

Regezi JA, Nickoloff BJ, Headington JT. Oral submucosal dendrocytes: factor XIIIa$^+$ and CD34$^+$ dendritic cell populations in normal tissue and fibrovascular lesions. J Cutan Pathol 1992: 19: 398–406.

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Accepted February 18, 1992.

Dermal dendrocytes, originally identified by Headington (1), have been recently characterized as factor XIIIa$^+$ dendritic cells of bone marrow origin that are found typically in the adventitia of dermal blood vessels and in the interstitial dermal connective tissue (2, 3). They are rarely found in the epidermis, and they are unrelated to other resident cells (Schwann cells, endothelial cells, melanocytes) of the skin (4).

The immunophenotype of dermal dendrocytes indicates that they represent a subset of the monocyte-macrophage system, and are a population of cells distinct from Langerhans cells (epithelium), indeterminant cells (connective tissue pre-Langerhans cells), interdigitating cells (thymus dependent areas of lymphoid tissue), follicular dendritic cells (germinal center and mantle zone of lymphoid follicles), and tissue macrophages (3–7). In addition to factor

Table 1. Dendritic cells and relatives.

	XIIIa	CD1	S-100	HLA-DR	CD14	CD34	CD45	MAC 387
Dermal dendrocyte I*	+	–	–	+	+	––	+	–
Dermal dendrocyte II*	–					+		–
Langerhans cell	–	+	+	+	+	–	+	–
Indeterminate cell	–	+	+	+	+	–	+	–
Interdigitating cell	–	–	+	+	+	–	+	+
Follic. dendritic cell	–	–	–	+	+	–	+	–
Monocyte	+	–	–	+	+	–	+	+
Macrophage	±**	–	–	+	+	–	+	+
Fibroblast	–	–	–	–	–	–	–	–
Vascular endoth. cell	–	–	–	+	–	+	–	–

* I-refers to XIIIa$^+$ dendrocytes, II-refers to CD34$^+$ dendrocytes.
** Some macrophages such as peritoneal macrophages are XIIIa$^+$.

XIIIa expression, dermal dendrocytes express leukocyte function-associated antigen (CD18), some monocyte-associated antigens (CD14, CD11b), some lymphocyte-associated antigens (CD4), and pan-leukocyte antigens (CD45). They also produce ICAM (intercellular adhesion molecule) and increased HLA-DR expression following gamma-interferon exposure. They neither express Langerhans cell-associated antigens (CD1) nor contain Langerhans cell granules. They do not express some pan-T cell antigens (CD2), some monocyte/macrophage antigens (CD11c, CD15, Mac 387), S-100 protein antigens, or factor VIII-related antigen (Table 1).

Factor XIII (subunits a and s) is a blood coagulation enzyme (protransglutaminase) that plays a part in the stabilization of fibrin in the clotting process. It is found extracellularly in plasma as a dimer of subunit "a" attached to a dimer of a carrier protein known as subunit "s". Intracellularly, factor XIII appears to be composed almost exclusively of subunit "a". Factor XIIIa has been demonstrated in megakaryocytes and platelets, peripheral blood monocytes, peritoneal macrophages, lymphoid "histiocytic reticulum" cells, and recently, dermal dendrocytes. Lymphocytes, fibroblasts, tissue macrophages, and mast cells do not express XIIIa (9, 11–13).

It has been suggested that factor XIIIa$^+$ dermal dendrocytes may function in maintaining the immunologic competence of the host. It has also been postulated that dermal dendrocytes significantly influence lymphocyte trafficking in the skin through the production of tumor necrosis factor (14, 15). This cytokine, known to induce keratinocyte production of interleukin-8 (T cell and neutrophil chemoattractant), and expression of ICAM (T cell – keratinocyte communication signal) appears to be a primary mediator for this immunologically important cell.

Dermal dendrocytes also appear to have a central role in the pathogenesis of some focal connective tissue proliferations. Factor XIIIa$^+$ cells have been identified as the predominate cell type in dermatofibromas (16, 17), and they represent a significant portion of the spindle cell population of early Kaposi's sarcoma (18, 19), though they may be absent in later stages (20). They have also been found in neurofibromas and malignant fibrous histiocytomas, but not schwannomas, fibromatosis, nodular fasciitis, and dermatofibrosarcoma (16, 21, 22).

Recently, antibody to CD34 antigen was shown to label dendritic and spindle cells of the reticular dermis, as well as endothelial cells of small blood vessels (23, 24). Antigen CD34 is a glycoprotein ordinarily found on human hematopoietic progenitor cells (lymphocytes, monocytes, granulocytes, platelets) (25).

CD34 appears to be located on a dendritic cell subset that is different from XIIIa$^+$ dermal dendrocytes. These cells are found predominantly in the reticular dermis and have, as yet, an undetermined function. That both endothelium and bone marrow precursor cells also express CD34 suggests that the biology of these cells is interrelated. The relationship between these CD34$^+$ dendritic cells and the XIIIa dendritic cells and other monocyte/macrophages is unknown.

CD34$^+$ staining has been described on the stromal spindle cells and endothelial cells of Kaposi's sarcoma (23, 26). It was suggested that rather than resulting from proliferation of fibroblasts, these lesions occur, in part, because of proliferation of CD34 positive vascular endothelial cells and spindle cells which come from a common stem cell.

The purposes of this study are to establish the presence of factor XIIIa$^+$ and CD34$^+$ dendritic cells in oral mucous membranes and to determine their distribution in normal tissue and in oral fibro-vascular lesions.

Material and methods

Formalin-fixed paraffin-embedded tissues were utilized in this study as all antigens studied are

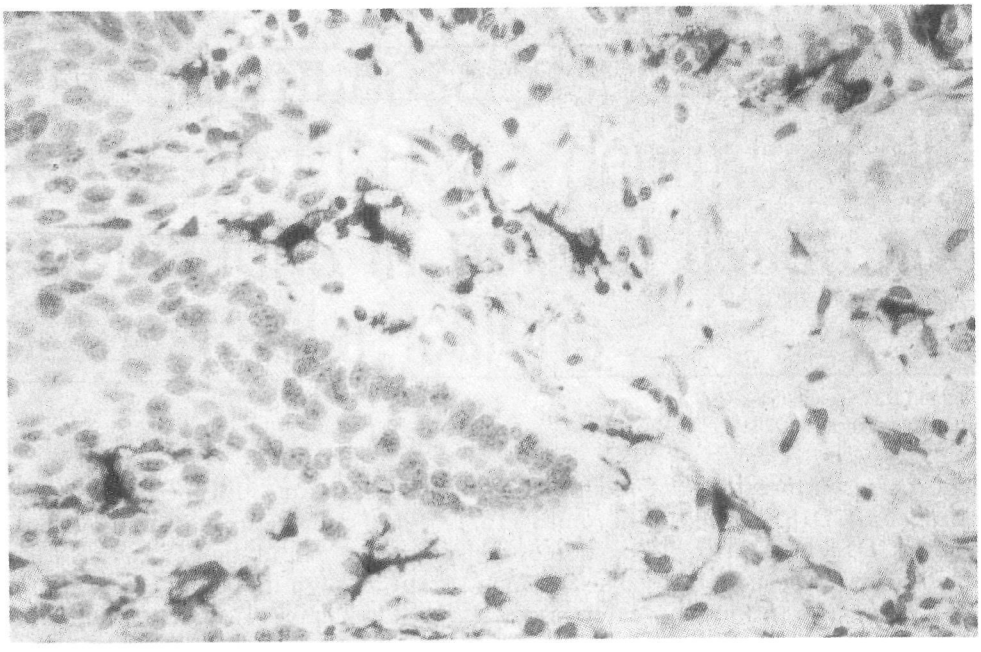

Fig. 1. Factor XIIIa$^+$ dendrocytes in lamina propria of the tongue. Epithelium to the left (×400).

resistant to routine processing. Sections of normal lingual tonsilar mucous membrane (5), peripheral fibromas with stellate (dendritic) cells (also known as giant cell fibromas) (5), peripheral fibromas with ossification (5), peripheral giant cell granulomas (3), gingival pyogenic granulomas (5), oral lymphangiomas (5), oral mucosal benign fibrous histiocytomas (5), idiopathic histiocytosis (Langerhans cell disease) (3), and nasopharyngeal angiofibromas (3) were mounted on adhesive coated glass slides for immunohistochemical staining. The angiofibromas were included because of the stellate cells and vascular stroma that comprise these lesions.

Antibodies to factor XIIIa (Calbiochem, La Jolla, CA, diluted 1:400), human progenitor cell antigen, CD34, (Becton-Dickinson, Mountain View, CA, HPCA-1, diluted 1:20), S-100 protein (Dako, Santa Barbara, CA, diluted 1:700), and monocyte/macrophage antigen (Dako, Santa Barbara, CA, MAC 387, diluted 1:100) were applied to dewaxed sections. Except for HPCA-1, sections were preincubated with trypsin. Following incubation with primary antibody, an avidin-biotin-peroxidase method was employed for identification of immunologic reactivity (Vectastain, Vector Laboratory, Burlingame, CA). Sections were developed in aminoethylcarbazole and counterstained with Mayer's hematoxylin. Normal rabbit serum and mouse myeloma proteins were substituted for primary antibody in negative controls. The XIIIa positive cell population of the various lesions included in this study was estimated by counting immunoreactive and non-reactive tumor cells (excluding endothelial cells and inflammatory cells) in five representative high power fields (400 ×).

Results

XIIIa in normal tissue – In all the normal lingual tonsilar mucous membrane biopsies and in the normal tissue adjacent to the tumors studied, factor XIIIa$^+$ dendritic and spindle cells were readily apparent (Fig. 1). Cells were dispersed in the interstitial connective tissue, with numbers generally grea-

Table 2. Immunoreactivity of oral connective tissue lesions.

	XIIIa	CD34	S-100	MAC 387
Normal muc. memb.	variable	endo./dendro.	Langerhans cells	macs
Periph. fibroma	10–30% pos	endothelium	few pos cells	neg
Periph. oss. fib.	5–10% pos	endothelium	few pos cells	neg
Periph. G.C. Gran.	0–5% pos	endothelium	5% pos cells	neg
Pyogenic granuloma	5–20% pos	endothelium	few pos cells	neg
Lymphangioma	neg	neg	not done (N/D)	N/D
Fib. histiocytoma	5–25% pos	endothelium	few pos cells	neg
Histiocytosis	neg	endothelium	80% pos	neg
Angiofibroma	10–20% pos	endothelium	few pos cells	neg

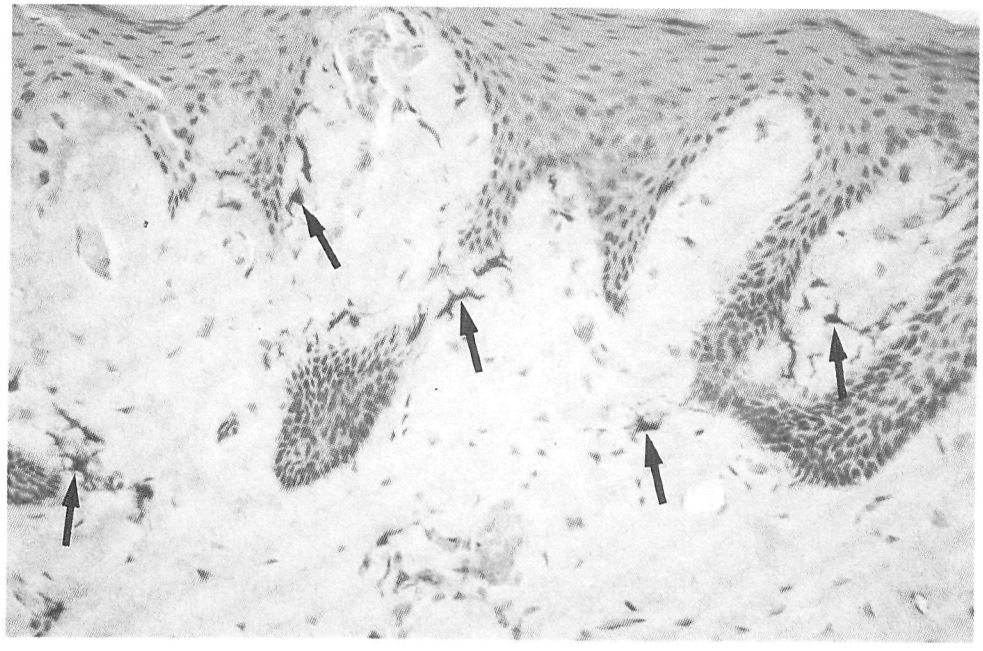

Fig. 2. Peripheral fibroma of gingiva exhibiting numerous factor XIIIa$^+$ dendrocytes (arrows) (×100).

ter in the lamina propria and subjacent connective tissue than in deeper tissues. Frequently, dendritic cells were seen closely approximating small vessels in an angiocentric pattern. In the perifollicular lymphoid tissue of the lingual tonsils, prominent XIIIa$^+$ dendritic cells were consistently seen. There were no positive cells in the germinal centers. Dendritic cells were noted between skeletal muscle bundles and within connective tissue septae of lingual salivary glands. Rarely were cells found in the epithelium. No positive staining was apparent in the cells making up the taste buds of the lingual tonsilar papillae. In normal tissue surrounding the tumors studied, XIIIa$^+$ cells were often prominent, particularly around vessels.

XIIIa in reactive lesions – With the exception of the Langerhans cell disease biopsies, XIIIa$^+$ cells were found within all the fibro-proliferative lesions studied. Numbers, however, varied within tumor groups, and between tumor types (Table 2). The morphology of the positive cells was spindle to dendritic, similar to those seen in normal tissue. Endothelial cells were non-reactive.

In the peripheral fibromas, in which stellate (dendritic) cells are prominent in H&E sections, stain-

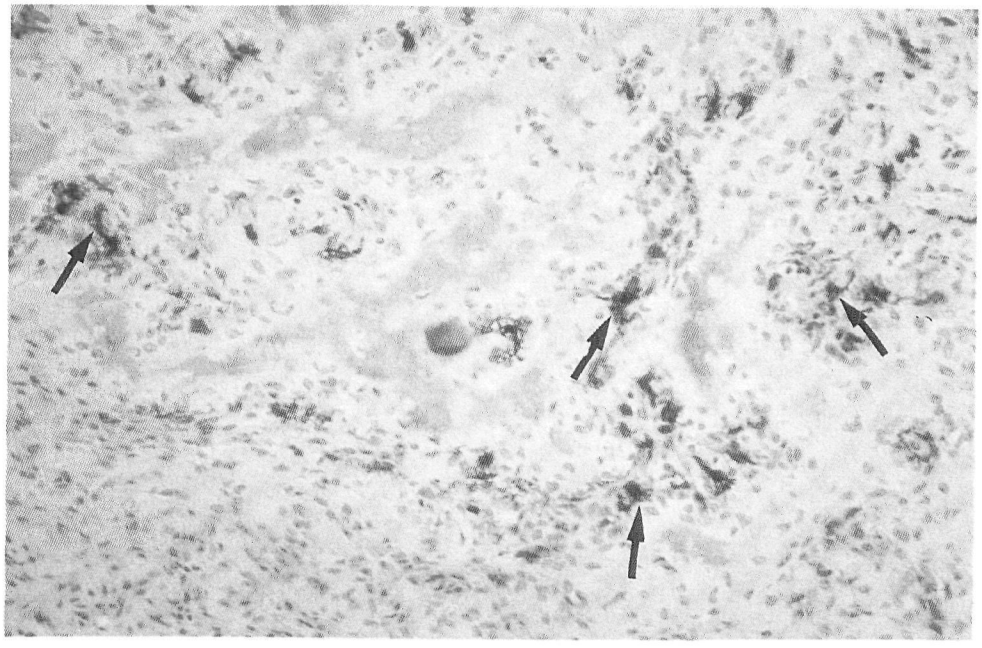

Fig. 3. Gingival peripheral fibroma with ossification showing numerous XIIIa$^+$ dendrocytes (arrows) adjacent to metaplastic islands of bone (×250).

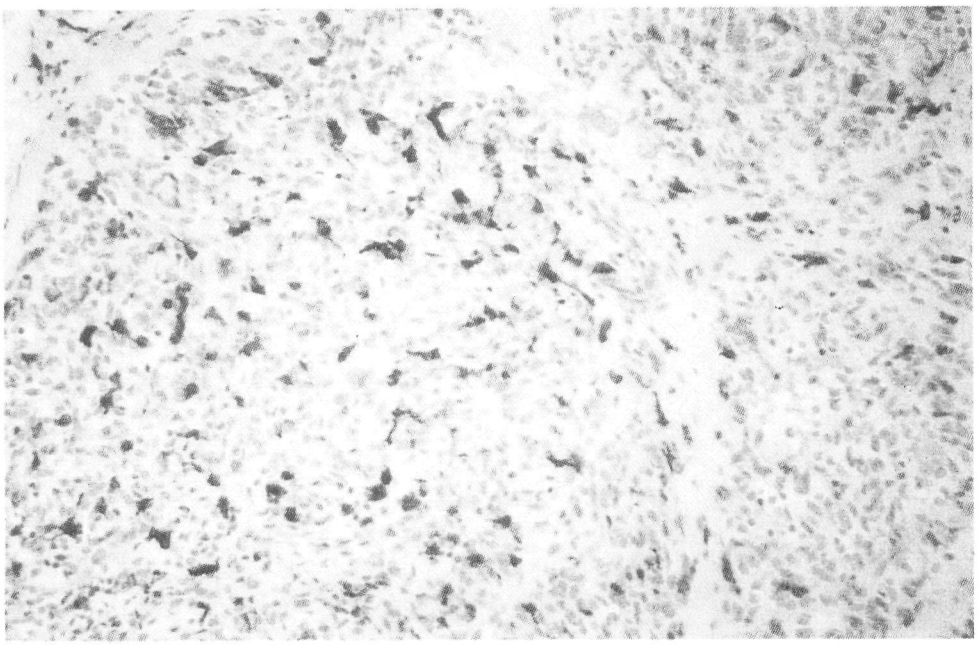

Fig. 4. Lobules of gingival pyogenic granuloma with abundant dark staining XIIIa$^+$ dendrocytes (×250).

ing was seen in only a minority of the cells, most frequently in the lamina propria (Fig. 2). Multinucleate dendritic cells were usually negative.

In peripheral fibromas with ossification, XIIIa$^+$ spindle and dendritic cells were found concentrated around islands of metaplastic bone (Fig. 3). They did not appear to be osteoblasts as they were not seen on the osteoid seams. Reactive bone found incidentally in some of the other tumors did not exhibit bone-associated XIIIa$^+$ cells.

Peripheral giant cell granulomas of the gingiva showed little XIIIa immunoreactivity within each lesion, though staining was intense in perivascular cells of surrounding tissue. In gingival pyogenic granulomas focal intense staining of non-endothelial interstitial cells was seen (Fig. 4). Endothelial cells of lymphatic vessels were uniformly non-reactive.

XIIIa in neoplasms – Benign fibrous histiocytomas showed significant intra-tumor staining. Cell morphology in these lesions was typically spindle. Though a patchy distribution of positive cells was the rule, one lesion exhibited diffusely distributed positive cells (Fig. 5). Tumor cells located at the periphery of the lesions often stained more intensely than more centrally located cells.

Fig. 5. Benign fibrous histiocytoma of the buccal mucosa showing intense XIIIa tumor cell staining at periphery (arrows) and faint positive staining centrally (above). Note positive staining of dendrocytes in supporting connective tissue (below) (×250).

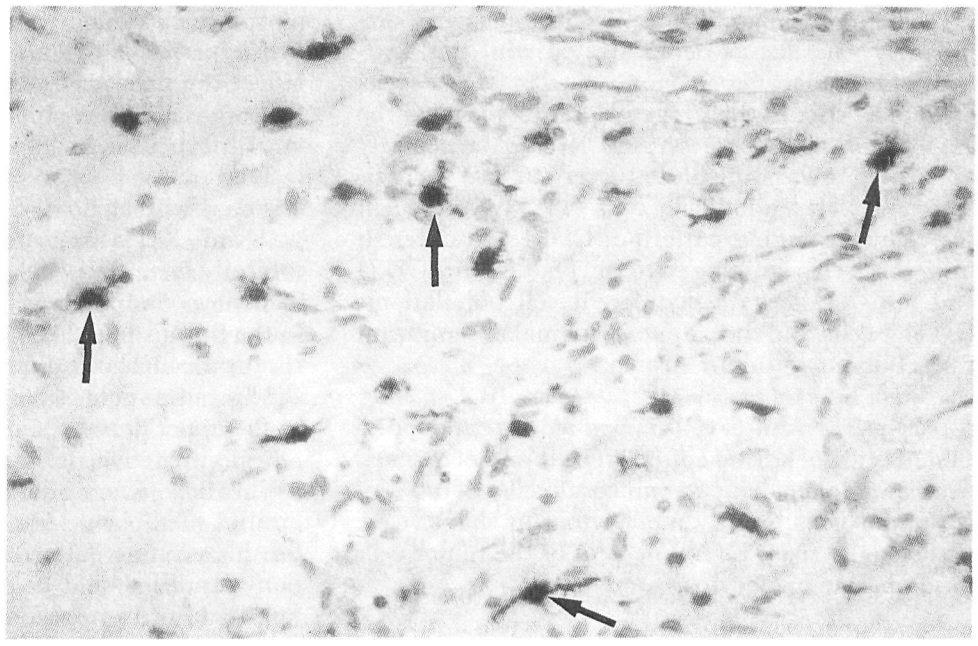

Fig. 6. Nasopharyngeal angiofibroma with scattered XIIIa$^+$ dendrocytes (arrows) (×400).

While the tumor cells of idiopathic histiocytosis were XIIIa negative, surrounding connective tissue contained abundant positive cells. In the nasopharyngeal angiofibromas, evenly distributed XIIIa positive dendritic cells were apparent, though only 10–40% of tumor cells were reactive (Fig. 6).

CD34 – Anti-CD34 did not stain the dendritic cells that were identified with anti-XIIIa. It did stain, however, endothelial cells of small blood vessels (with the exception of lymphoid associated high endothelial venules) in both normal tissue and tumor tissue. Endothelium lining larger vessels was typically non-reactive, though spotty staining was occasionally seen. Lymphatic endothelium in lymphangiomas was non-reactive. In the tumors almost all positive cells appeared to be lining blood vascular spaces. Occasional CD34$^+$ dendritic and spindle cells that were not vessel associated, were seen in deeper levels of normal submucosa in many of the biopsy specimens. These CD34$^+$ dendritic cells were much more frequent in skeletal muscle that was occasionally found at the deep margin of the biopsy specimen (Fig. 7). The dendritic cells were frequently seen in close physical relationship to muscle-associated capillaries.

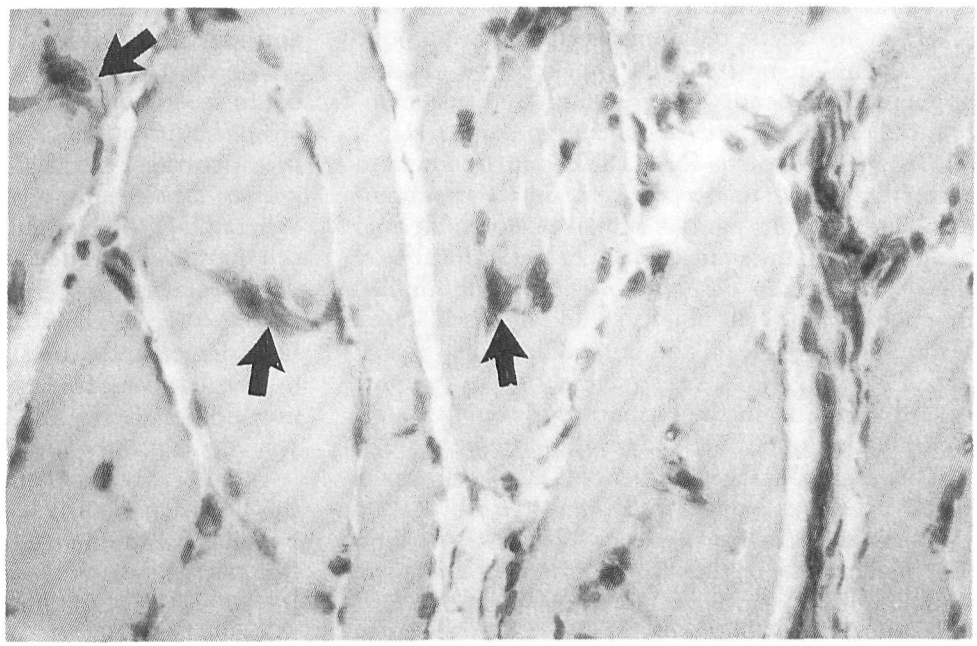

Fig. 7. Submucosal skeletal muscle exhibiting several CD34$^+$ dendrocytes (arrows) (×400).

One of the benign fibrous histiocytomas was surprisingly vascular as demonstrated with this antibody. Only rarely could non-vascular $CD34^+$ cells be found. Also, in the pyogenic granulomas and the angiofibromas, where vessels were particularly abundant, it was difficult to be certain that all positive cells were endothelial cells (14). In any event the cellular staining pattern of CD34 was different from the XIIIa staining pattern. That is, anti-CD34 and anti-XIIIa stained different cell populations. $CD34^+$ cells did not appear to make significant contributions to tumor stroma.

S-100 protein – Anti-S-100 stained a different population of cells; dendritic epithelial cells and occasional oval-spindle-dendritic submucosal cells. $S\text{-}100^+$ intra-tumor cells, mostly monocytoid in shape, were occasionally seen. Eighty percent of the tumor cells in idiopathic histiocytosis were $S\text{-}100^+$.

MAC 387 – MAC 387 was responsible for staining of tissue macrophages and blood monocytes. Tumor cells were non-reactive, but occasionally scattered macrophages were seen. Mucosal and submucosal dendritic cells and endothelial cells were MAC 387^-.

Discussion

From this study it is apparent that factor $XIIIa^+$ dendritic cells are normal residents in oral mucous membranes. These submucosal dendrocytes, which exhibit an immunologic phenotype of $XIIIa^+$, $CD34^-$, S-100 $protein^-$ MAC 387^- are found generally in association with either collagen, blood vessels, or lymphoid tissue. The lymphoid-associated cells may be identical to the previously described $XIIIa^+$ "histiocytic reticulum" cells of lymph node (13). $CD34^+$ dendritic cells appear to be another population of dendrocytes in oral mucous membranes. They express a phenotype of $XIIIa^-$, $CD34^+$, S-100 $protein^-$ MAC 387^- and are found in greater numbers in deeper aspects of the submucosa. These results parallel similar studies of dermal dendrocytes in the skin (1–4, 23). The significance of these oral mucosa observations lies in the implied function of these cells in normal and diseased states. From the morphologic and immunologic features, it appears that $XIIIa^+$ cells have a role in immune surveillance and in the formation of some tumors. The function of $CD34^+$ cells is more obscure.

The relatively large number of $XIIIa^+$ cells in the reactive lesions studied indicates that there is a pathogenetic role for dendrocytes in these lesions. The mechanism of their proliferation is unknown, although it may be related to antigenic stimulation. The appearance of the $XIIIa^+$ cells in the neoplasms included may be due to concomitant dendrocyte hyperplasia by an unknown stimulus, or it may reflect the presence of a hybrid tumor cell population whose XIIIa expression is influenced by the focal effects of inductive cytokines (27).

That only a portion of the cells in the peripheral fibromas with stellate (dendritic) cells were reactive with anti-XIIIa indicates the presence of a phenotypically heterogeneous dendritic cell population. These lesions appear to be the oral histologic analog to the fibrous papule of the nose, which also exhibit similar histochemical features (28). Stellate cells of the fibrous papule of the nose are $XIIIa^+$, especially in the upper dermis, and multinuclear cells are usually non-reactive. In the peripheral fibromas with ossification where dendrocytes are concentrated around metaplastic bone, no reason was apparent for this staining pattern. Additional studies of other bony lesions should be done. Pyogenic granulomas appear to be composed of two immunologically different cell types: $XIIIa^+$ interstitial cells and $CD34^+$ endothelial cells. Whether or not one cell can give rise to the other is to be determined.

$XIIIa^+$ cells, which occur in significant numbers in oral benign fibrous histiocytomas, may have an important role, either primarily or secondarily, in the development of these lesions. These tumors may be derived directly from $XIIIa^+$ dendrocytes, or from precursor cells that can differentiate into dendrocytes. Alternatively, these tumors may be formed by other connective tissue cells that can be induced to express XIIIa antigens by some, as yet, undetermined factor(s).

The finding of significant numbers of $XIIIa^+$ cells in all the neoplasms studied (5 benign fibrous histiocytomas, 3 angiofibromas) suggests that there may be diagnostic utility associated with the use of this antibody. In the skin, dermal dendrocytes were present in dermatofibromas and Kaposi's sarcoma, but not in several other connective tissue tumors (4, 16–18). Whether or not factor XIIIa antigen expression is consistently restricted to certain types of oral connective tissue tumors remains to be determined. Where diagnostic confirmation of equivocal spindle cell tumors is needed, factor XIIIa staining may prove valuable.

In the skin a $CD34^+$ dendritic cell population has been demonstrated in the dermis, especially the reticular dermis. CD34 positivity has also been found in endothelial cells and in spindle cells around vessels, sweat glands, and hair follicles (23).

In all oral biopsies, endothelial cells of blood vessels were consistently labeled with anti-CD34, while lymphatic endothelial cells, as in the lymphangiomas, were consistently non-reactive. Since the endothelial cells of Kaposi's sarcoma have been reported to be $CD34^+$, (23, 26) one could conclude that this

tumor is more closely related to blood vascular endothelium than lymphatic endothelium as previously postulated (29).

$CD34^+$ dendritic and spindle cells not associated with vessels were sparse in the upper and middle submucosa, but were frequently seen in skeletal muscle and interfascicular connective tissue. While double staining (XIIIa and CD34) was not done, the distribution of these cells was markedly different, supporting the notion that there were two phenotypically-different dendritic cells. There was no convincing evidence that CD34 positive cells contributed significantly (other than endothelium) to any of the lesions studied, though it has been suggested that they may play a role in the development of cutaneous Kaposi's sarcoma (18, 19). The biologic function of this phenotypically distinct dendrocyte population in mucous membranes is unknown.

The lack of S-100 reactivity by $XIIIa^+$ and $CD34^+$ submucosal dendrocytes, and their submucosal location indicate that they represent dendritic cell populations that are distinct from Langerhans cells. Also, their non-reactivity to MAC 387 and their dendritic morphology show that they are different from macrophages, though they may be functionally related.

From this study, concluding observations can be summarized as follows:

* Normal submucosa contains at least two dendrocyte populations (XIIIa and CD34) (further characterization needs to be done to confirm identity with dermal dendrocytes).
* Submucosal dendrocytes are phenotypically different from macrophages and Langerhans cells.
* $XIIIa^+$ dendrocytes and spindle cells make up a significant part of the cellular population of normal oral submucosa. They are found in collagen-associated, vessel-associated, and lymphoid-associated relationships.
* Peripheral fibromas with stellate cells (the probable oral counterpart of the fibrous papule), peripheral fibromas with ossification, and pyogenic granulomas are composed, in part, of $XIIIa^+$ dendritic and spindle cells.
* Benign fibrous histiocytomas, and nasopharyngeal angiofibromas are composed of a phenotypically heterogeneous cell population, of which $XIIIa^+$ cells are a minor component.
* $CD34^+$ dendritic and spindle cells are residents of deep submucosa, especially in association with skeletal muscle.
* Blood vascular endothelium is $CD34^+$; lymphatic endothelium is $CD34^-$.
* Other than blood vascular endothelium, $CD34^+$ cells are not found in significant numbers in the tumors studied.

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