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Molecular mapping of Factor XIIIa-enriched dendrocytes in the skin (Review)

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Abstract. The human dermis contains a series of dendritic cells which express different phenotypes including Factor XIIIa immunoreactivity. This compound is related to a blood coagulation factor participating in angiogenesis, in the final stages of the clotting cascade and in wound healing. In normal skin, Factor XIIIa is expressed in specific dermal dendrocytes (DD) derived from the monocyte/macrophage lineage or from a mesenchymal origin. DD are located predominantly around the microvasculature in the adventitial dermis, at the dermo-epidermal junction, and around skin appendages, but normally not within the epidermis. Increased numbers of Factor XIIIa$^+$ DD are present in a host of specific cutaneous inflammatory and fibrotic conditions. In tumor pathology, immunophenotypic differences are found between dermatofibromas and other fibrohistiocytic entities, most notably dermatofibrosarcoma protuberans. In addition, Factor XIIIa$^+$ DD are likely to be involved in the progression and regression of some malignancies including cutaneous melanoma and basal cell carcinoma.

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1. Introduction

The dermis contains dendritic cells interacting with the microvasculature (1,2). Dermal dendrocytes (DD) exhibit some degree of immunophenotypic and functional heterogeneity (3,4). Morphologically, they may be confused with other cells such as fibroblasts and mast cells. In the skin, DD can be distinguished by 3 main immunohistochemical markers: the enzyme Factor XIIIa, CD34 antigen and thrombomodulin (5,6).

Factor XIII is a blood coagulation proto-transglutaminase (7), which becomes an activated component during the final stages of the clotting cascade as a result of the interaction with thrombin and Ca^{2+}. Factor XIII plays a key role in fibrin stabilisation. The plasma enzyme is a heterotetramer composed of paired A and B sub-units (A2B2). In contrast, in the cellular form, Factor XIIIa is a homodimer of A sub-units (A2) lacking the B sub-units. The gene coding for the A and B sub-units are mapped on the chromosomes 6p24-25 and 1a31-32.1, respectively. Cells of bone marrow origin are believed to be the main source of the sub-unit A in plasma Factor XIII. Hepatocytes are also involved in the same process. The sub-unit B of plasma Factor XIII is synthesized in the liver.

In addition to the functional homeostatic role in clot formation, Factor XIII is significant in wound healing (8) and embryo implantation (9), which involve angiogenic pathways (10). In wound healing, Factor XIII is believed to be central to reducing vascular endothelial permeability.

2. Factor XIIIa$^+$ cells

Immunohistochemical identification of Factor XIIIa in tissue sections has been available for ~20 years (1,11,12). Factor XIIIa$^+$ cells were presented in various organs including skin, esophagus, stomach, small and large bowels, bladder, lungs and kidneys. Lower quantities of Factor XIIIa$^+$ cells are found in the liver, thyroid, testis and spleen (13). Factor XIIIa is also expressed in human megakaryocytes, platelets, peripheral blood monocytes, peritoneal-alveolar-brain macrophages, follicular dendritic reticulum cells of reactive lymphoid follicles, tumor-associated macrophages, encapsulated lymphoid structures, lymph nodes of Hodgkin disease, primary and metastatic brain tumors, as well as in the placenta, uterus and prostate (13). The elevated numbers of Factor XIIIa$^+$ cells in such tissues suggest they have an important role in immune responses.

In the skin, Factor XIIIa$^+$ DD are normally confined to the dermis, with greater quantities present within the papillary dermis, at the dermo-epidermal junction, and in loose areolar connective tissue around the appendages, particularly the pilosebaceous units and abutted to vessels (1,12-14). High numbers of these cells are present in the septa between fat lobules. In contrast, they are scattered within the reticular dermis.

The antigenic epitope of Factor XIIIa is localised predominantly in the cytoplasm of the specific DD, with some membraneous labeling (14). Factor XIIIa$^+$ DD exhibit structural aspects depending on their location in the dermis. At the dermo-epidermal junction, they appear as moderately larger demarcated DD, with prominent cell bodies and tapering cell processes (15), most of which are orientated towards the epidermis. Conversely, Factor XIIIa$^+$ DD located deeper in the dermis are narrow and the dendritic processes less prominent. The ultrastructural features of DD encompass rows of pinocytic vesicles beneath the plasma membrane, small dense fibronexus-like plasma membrane plaques, gap junctions and some phagolysosomes (15-20).

In vitro, DD are considered to be established by a culture of peripheral blood monocytes in the presence of granulocyte macrophage-colony stimulating factor (GMCSF) and interleukin-4. The colocalization of α1 (XVI) collagen and Factor XIIIa inside DD, and their coordinate induction in CD14$^+$ monocyte-derived dendritic cells *in vitro* is physiologically important (21). It appears that α1 (XVI) collagen is constitutively expressed by most DD and dendritic cells differentiated from peripheral blood monocytes *in vitro*. Type XVI collagen expressed in Factor XIIIa$^+$ DD probably forms intermolecular cross-linking through the NC11 domain. The reaction catalyzed by Factor XIIIa contributes to the structural integrity and tensegrity of Factor XIIIa$^+$ dendritic cell-rich tissues.

3. Factor XIIIa$^+$ dendrocytes during fetal life

In the fetus, Factor XIIIa$^+$ cells are most abundant in the dermis and other connective tissues (22,23). Numerous large, stellate cells in placental villi, deciduas, and chorionic membranes express Factor XIIIa at 7-9 weeks of the gestational age, before the onset of fetal hematopoiesis (23). Factor XIIIa immunolabeling appears heterogeneous in the early and late fetal tissues, in rounded and dendritic cells. Some cells express Factor XIIIa and certain monocyte markers. They are identified in close association with blood vessels and lymphoid organs in the late fetus and in the placental villi at the end of gestation. Other rounded and dendritic cells express Factor XIIIa but not monocyte markers. They are found in fetal connective tissues at all gestational ages as well as after birth. These observations suggest that two Factor XIIIa$^+$ cell populations co-exist (23). One DD population present at all developmental ages does not express monocyte markers, and probably differentiates *in situ* from the primitive mesenchyme. The other DD population appears mainly after the initiation of fetal hematopoiesis, co-expressing some monocyte markers, showing HLA-DR positivity and being capable of antigen presentation.

4. Factor XIIIa$^+$ dendrocyte immuno-phagocytic function

DD appear heterogeneous according to their immunophenotype, stage of maturation and function (24,25). Cells of the skin exhibit varied presentations which are influenced by local tissue microenvironmental conditions (26,27). Thus, DD may represent peculiar types of mesenchymal cells that are sufficiently plastic to express different phenotypic markers at specific stages of the differentiation and/or proliferation cycle, and to alter their morphology based on the extracellular matrix and neighbouring cells (28,29).

DD of bone marrow origin are CD45$^+$ (28). They exhibit particular histoenzymatic and immunohistochemical features sharing similarities with antigen-presenting cells (HLA-DR$^+$, LFA1$^+$ and HLA-DQ$^+$) (30). They are quite distinct from fibroblasts (3,11,13,14). Approximately 80% of DD are positive for myelomonocytic markers CD13 and CD33, but there is no CD15 immunoreactivity. Unlike Langerhans cells they do not express CD1a and are phagocytic (11,31,32). Some sub-populations share common phenotypic features with monocytes and macrophages (CD11b$^+$, CD11c, CD14$^+$, CD32$^+$ and CD36$^+$). Expression of the surface Fc and complement receptors is critical for phagocytosis since they are involved in particle binding and uptake. DD do not express Fc γ RII which enhances phagocytosis of opsonized particles. Furthermore, the majority of DD express the complement receptors type III and IV, which are involved in the uptake of C3b- or iC3b-coated microorganisms.

Factor XIIIa expression is a marker for alternative macrophage activation, while the absence of Factor XIIIa in monocyte-derived macrophages is an indicator of their inactivated state (33).

5. Factor XIIIa$^+$ dendrocyte tensegrity

The intracellular role of Factor XIIIa remains comparatively unexamined. This molecule belongs to the transglutaminase family. The activation mechanism for this intracellular form of Factor XIIIa is unknown, but Factor XIIIa has been suggested to undergo conformational changes induced by the ionic environment rather than by proteolysis. Such an activation mechanism is effective at high ionic strength. When the intracellular Ca^{2+} concentration becomes elevated, the slow progressive non-proteolytic activation of Factor XIIIa occurs. Thus, the native zymogen is transformed into the active transglutaminase. In some circumstances, a low Ca^{2+} concentration in the physiological range of plasma is sufficient to support the process. Different cytoskeletal proteins including type XVI collagen (21) can serve as substrates for Factor XIIIa, suggesting that Factor XIIIa plays a significant role in cell tensegrity and cellular functions characterized by intense cytoskeletal reorganization.

Cell tensegrity represents the influence of mechanical stress on the cell shape by modelling its cytoskeleton. Factor XIIIa$^+$ DD exhibit striking changes in their appearance according to the intrinsic mechanical forces present in the skin (27,29,34, 35). They are rarefied and thin in the loose connective tissue of Ehlers-Danlos syndrome (27,34), but appear plump in acromegaly (29). During tissue expansion in animals, the expression of Factor XIIIa appears to be completely abolished (36).

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ly, methotrexate was found to severely alter DD giving them a ballooned appearance (37). This effect is likely to be related to the direct influence of the drug on the cytoskeleton (38).

6. Factor XIIIa$^+$ dendrocytes in dermatitides

Factor XIII is of potential significance as a modulator of inflammation. Some arguments also refer to local consumption and/or loss of Factor XIII within the inflamed tissue during acute episodes of inflammatory bowel diseases. Generally, Factor XIIIa$^+$ cells in pathological skin conditions can be split into expression in inflammatory and fibrosing conditions, and in neoplastic pathology. Inflammatory macrophages may release or express Factor XIIIa at their surface. The important role ascribed to Factor XIII in inflammation is related to the fact that several adhesive glycoproteins are transglutaminase substrates. The enzyme may play an important role in cell adhesion and migration.

In terms of inflammation Factor XIIIa expression is elevated in several conditions including spongiotic dermatoses, lichen planus and psoriasis (1,5,11,13,39-43). In acute and chronic graft-versus-host disease (GVHD), expression of Factor XIIIa in DD is altered and usually increased (16,19,25,42,44,45). Migration of Factor XIIIa$^+$ cells into the epidermal compartment has been reported in chronic plaque psoriasis in association with other inflammatory cells (13). Chronic sun exposure and PUVA therapy are responsible for the same phenomenon (46,47). This feature is not limited to a few inflammatory diseases as it is commonly found in mycosis fungoides (48).

Toxic epidermal necrolysis (Lyell syndrome) is another example in which Factor XIIIa$^+$ DD are numerous (19,49-52). In this syndrome, a contrasting feature is present in lymph nodes where the Factor XIIIa$^+$ cells are rarefied (53).

It has been postulated that DD significantly influence lymphocyte migration in the skin through TNF-α production (49-51). This cytokine induces the keratinocyte production of interleukin-8 (T cell and neutrophil chemoattractant) and ICAM expression (T cell-keratinocyte communication signal). Thus, this mechanism appears to be an important aspect of DD function (54).

In leukocytoclastic vasculitis, Factor XIIIa-positive DD abutted to the involved microvasculature are altered giving rise to the features of dendrocytoclasia (54). In contrast, numerous normal-looking Factor XIIIa$^+$ DD accumulate in chronic erythema elevatum diutinum (43).

Some drugs appear to increase the size and number of Factor XIIIa$^+$ DD. Among them, etretinate, retinoic acid and imiquimod show activity on DD in the papillary dermis (56-59). Imiquimod appears to be markedly ineffective against tumoral lesions lacking a regular amount of Factor XIIIa$^+$ DD (60,61). This suggests that these cells participate in the drug-induced release of the cytokine storm-inducing tumoral regression. Cyclosporin is another drug which can alter the presentation of Factor XIIIa$^+$ DD (62).

7. Factor XIIIa$^+$ dendrocytes in phagocytic disorders

One of the intracellular functions of Factor XIIIa may be related to receptor-mediated phagocytosis. Macrophages bind α2-macroglobulin protease complexes which are known to be a substrate for plasma Factor XIII (63). There is evidence showing that ligand-receptor binding and the internalization of α2-macroglobulin complexes require transglutaminase activity. Increasing phagocyte activity is strongly associated with the expression of Factor XIIIa (63). Monocytes from Factor XIIIa-deficient patients show an impaired capacity to phagocytosis, while their locomotion remains normal. Among the steps of the phagocytic pathway, the mechanism of internalization of particles is most affected by the lack of Factor XIIIa (64).

Two further observations are suggestive of the Factor XIIIa involvement mechanism of phagocytosis. Peritoneal macrophages show condensation of Factor XIIIa in the pseudopodia and around phagocytotic vesicles. However, human myelomonocytic cell lines, which are incapable of phagocytosis do not express Factor XIIIa. During their differentiation induced by phorbolester, these cells demonstrate increased phagocytosis in parallel with the expression of Factor XIIIa. Ultrastructural studies have also demonstrated DD activation with enlarged endoplasmic reticulum and collagen fiber and mast cell granular phagocytosis in pathological conditions (31). These include toxic epidermal necrolysis and graft-versus-host reaction (19). In dermal melanoderma, melanophages express Factor XIIIa (15,32).

Diverse tumoral conditions accumulate cells of this lineage which show variable levels of the activation of phagocytosis. Xanthogranulomas (64), nodular histiocytosis (65) and reticulohistiocytomas (66,67) are typical examples.

8. Factor XIIIa$^+$ dendrocytes in fibroplasia

Factor XIIIa has a diagnostic value in certain fibrosing disorders. DD play a central role in the pathogenesis of some disorders associated with focal connective tissue hyperplasia. They represent the predominant cell type in dermatofibroma, dendrocytoma, histiocytoma, angiohistiocytoma and epithelioid cell histiocytoma (68-77). However, there is an array of patterns that ranges from sporadic to diffuse expression of Factor XIIIa. An immunoelectronmicroscopic examination of Factor XIIIa$^+$ DD in dermatofibromas reveals that these cells display moderate to abundant rough endoplasmic reticulum, lipid droplets and/or bundles or myofilaments in varying proportions. There is also evidence of macular adherence connections between neighbouring cells. Most likely, the variability in Factor XIIIa expression in dermato-fibroma is the result of the age of the lesion. Similarly, this appears to be true in morphoea (78,79). Variability of expression suggests that the Factor XIIIa expression in dermal cells is a facultative function induced by undefined factors that are released locally (80). It is possible that the transforming growth factor (TGF)-ß1 is released by Factor XIIIa$^+$ DD (81). A vicious cycle ensues as TGF-ß1 regulates dendritic cell maturation leading to further recruitment and activation of DD and more TGF-ß1 production resulting in tissue fibroplasia.

A similar mechanism is probably operative in disorders such as scleromyxoedema and nephrogenic systemic fibrosis (82). In early lesions, a marked thickening of the dermis is accompanied by the accumulation of cells with long dendritic processes. In fully developed cases, they are often associated

with histiocytes and stellate Factor XIIIa$^+$ DD. In addition, CD34$^+$ DD with the dendritic processes form a dense network. It has been suggested that the CD34$^+$ cells are circulating cells that have been recruited to the dermis. There is also an increased number of CD68$^+$ and Factor XIII$^+$ DD, some of which are positive for the two markers (83-87).

Factor XIIIa$^+$ DD may be almost absent in sclerotic areas associated with benign and malignant neoplasms (70,78,88). The connective tissue built up *in epulis* show changes at different stages and Factor XIII is detected in monocyte-derived tissue macrophages, which are widely and homogeneously distributed in granulation tissue. During the fibrotic process, tumor-associated macrophages (TAMs) corresponding to Factor XIIIa$^+$ cells continuously decline in number. They are only recognized at the periphery of fibrosing foci and their morphological appearance alters from a stellate to spindle shape (89). In other conditions including collagenomas, the solitary fibrous tumor of the skin and dermatofibrosarcoma protuberans, Factor XIIIa$^+$ DD are reduced or absent (72,88-91). Hence, these cells probably play a role in the regulation of fibrosing processes (18,78).

An altered cytokine expression probably increases Factor XIIIa expression, particularly in T cell-mediated mycosis fungoides (48,92). Its absence in other cutaneous lymphomas corresponds with aggravation of the disease.

9. Factor XIIIa$^+$ dendrocytes in wound healing

Factor XIII may be a critical transglutaminase in connective tissue homeostasis and the repair process (93-97). Impaired wound healing observed in patients with homozygous Factor XIII deficiency suggests that the normal mechanism of wound healing and tissue repair requires this compound. Factor XIIIa not only stimulates fibroblast proliferation *in vitro* but is also a significant regulator of collagen biosynthesis by these cells (98,99). Fibroblasts then produce growth factors, collagen, elastin and other extracellular matrix components important in matrix remodelling and repair.

Factor XIIIa$^+$ DD have been shown to be related functionally and spatially to mast cells. They increase in number following mast cell degranulation. This has been linked to the release of TNF-α, a predominant pre-formed cytokine in human mast cell granules (17). Keratinocytes and DD are other sources of TNF-α in the skin (100). Thus, exogenous threats that directly impact the skin (such as trauma), endogenous stimuli delivered to the skin from the blood stream (e.g. drug metabolites and immune complexes) or pathological events that can trigger TNF-α producing cells may stimulate Factor XIIIa expression by DD. In this way, DD may induce the proliferation of their own population by autocrine and paracrine pathways.

10. Factor XIIIa$^+$ dendrocytes in neoplasms

Factor XIIIa$^+$ DD are found in fibrovascular lesions including fibrous papules of the nose, acquired digital fibrokeratomas, angiofibromas and oral fibromas (80,98,101-106). Factor XIIIa is possibly acting as a growth factor in these tumors, or these neoplasms are releasing an undefined stimulus. This is also the case in desmoplastic neoplasms (107). Increased numbers of Factor XIIIa$^+$ cells are often found at the base or surrounding most invasive cutaneous neoplasms (108-110). Such cells are often negative for conventional macrophage markers such as CD68. In our experience, Factor XIIIa$^+$ DD are numerous, abutting on and infiltrating most basal cell carcinomas and thin malignant melanomas (108). In contrast, they were present in only low numbers or even absent in thick primary malignant melanomas and their metastases (109-111). Circumstantial evidence linked the density of Factor XIIIa$^+$ dendritic cells and a low proliferative rate of neoplastic cells in malignant melanoma. Thus, Factor XIIIa$^+$ DD may not be passive in this neoplasm. Their function may differ based on whether they are located in the stroma or inside the neoplasm. Intratumoral DD may exert a growth-restricting role. In contrast, stromal DD may be involved in the invasiveness and metastatic spread of the cutaneous malignancies.

The expression of Factor XIIIa in spindle-shaped cells in Kaposi disease may be of significance. Kaposi disease is an Herpes VIII-induced multifocal neoplasm involving various organs. It is possible that a DD presence is important to the angioproliferative response in this particular condition (103,104,112).

Malignant fibrous histiocytomas and atypical fibrohistiocytomas exhibit Factor XIIIa expression in cells to a variable degree. It was assumed that since the neoplasms exhibit a wide spectrum of histological appearances, all of which are a variation of spindled fibroblast-like, undifferentiated and histiocytic or histocyte-like cells. Therefore, the Factor XIIIa$^+$ cells represent different levels of fibrohistiocytic differentiation (113,114).

Factor XIIIa is widely expressed in several tumor types belonging the series of non-Langerhans cell histiocytoses, such as xanthoma disseminatum and xanthogranulomas (115-117).

Among neural neoplasms, neurofibromas are enriched in Factor XIIIa$^+$ DD (118,119). Factor XIIIa has been reported to be positive in cellular neurothekeomas (120-122), a relatively rare benign cutaneous neoplasia frequently occurring in young adults on the head and neck. Factor XIIIa$^+$ cells have also been reported in granular cell tumors of the skin (123). Most of these neoplasms are derived from Schwann cells. The presence of Factor XIIIa$^+$ cells in granular cell tumors of the skin suggests that these tumors are an exception in the group of Schwannomas. The acral myxo-inflammatory fibroblastic sarcoma normally reveals Factor XIIIa immunoreactivity (124).

Extravascular fibrin deposition is frequently observed within and around neoplastic tissue and has been implicated in various aspects of tumor growth. In areas of fibrin deposition, TAMs may release or express Factor XIII at their surface. This relationship strongly suggests that Factor XIIIa secreted by intact cells or released from damaged TAMs is involved in the stabilization of intratumoral fibrin network, which facilitates the tumor-matrix generation and tumor angiogenesis. Factor XIIIa$^+$ monocyte-derived TAMs prevail over all other cell types at the site of intratumoral fibrin formation in different malignant tumors and are strongly attached to the fibrin strands. Factor XIII expressed on the surface of TAMs or released from damaged cells may have a significant role in

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11. Conclusion

The precise role of DD in the skin remains to be elucidated in different reactive or tumoral conditions. These cells may be increased or modified, and non-immunocompetent cells may also express intracellular Factor XIIIa in response to an altered cytokine network. In these abnormal conditions, Factor XIIIa$^+$ cells in the dermis belong to largely heterogeneous populations. The cytokine TNF-α appears to play a prominent role in Factor XIIIa expression by dermal cells. The function of DD may be mainly related to the phagocytic pathway, and to connective tissue homeostasis. This means that Factor XIIIa$^+$ cells may have different stages of maturation/activation with a transitional state of differentiation. Factor XIIIa$^+$ cells may represent multiple cell types with a common expression of a ubiquitous enzyme with some of the Factor XIIIa$^+$ cells being antigen-presenting and others non-inflammatory. Thus, there are phenotypic and functional (80) subsets of Factor XIIIa$^+$ dermal cells. For example, they express either CD1a or CD14 or have a variable expression of HLADR (101). It is possible that Factor XIIIa is a marker expressed only at certain phases of development of the cells of Langerhans lineage, perhaps in relation to cytokines predominant in the dermis as opposed to the epidermal microenvironment (102).

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