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Immunohistochemical Expression of Cathepsin L in Atopic Dermatitis and Lichen Planus

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Abstract

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Background:

Cathepsin L is a member of papain superfamily. It seems to promote T-cell survival, selection maturation in the thymus and enhance the antigen presentation. Cathepsin L plays an important role in tumor necrosis factors (TNF- α) induced cell death. Also it degrades the tight junction between cornedosomes in the epidermis. Elevated expression of cathepsin L has been found in many inflammatory and neoplastic diseases.

Objective:

The aim of this study was to determine immunohistochemical expression of cathepsin L in atopic dermatitis (AD) and lichen planus (LP) patients in order to evaluate its role in the pathogenesis of both diseases.

Materials and Methods:

This study included 15 patients with AD (Group I), 15 patients with LP (Group II), in addition to 10 healthy skin specimens served as controls (Group III). Punch biopsies were taken from lesional skin of the patients and controls for immunohistochemical detection of cathepsin L expression.

Results:

Highly significant increase was found in cathepsin L expression in AD and LP patients compared to controls [$P = 0.001$].

Conclusion:

Cathepsin L could be implicated as an important protease in the pathogenesis of AD and LP. It could be a useful marker for assessing AD severity.

Keywords: *Atopic dermatitis, cathepsin L, lichen planus and proteases*

What was known?

Cathepsin L is the cysteine protease which is considered as one of the most powerful endopeptidase. Increase in protease activity occurs in lichenoid and eczematoid epidermis which may play critical role in the pathogenesis of both diseases. Given the known effects of cathepsin L expression in AD and LP, it seems

appealing to try targeting cathepsin L in AD and LP patients with cathepsin inhibitors, which might provide new hopes added for treating both diseases.

Introduction

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Cathepsins, belonging to the lysosomal cysteine proteases, were particularly emphasized for their activity in important biological functions, such as proteolytic processing of proenzymes, antigen presentation, inflammation, hormone maturation, fertilization, tissue remodeling, bone matrix resorption, cell proliferation, differentiation, apoptosis and degradation of the extracellular matrix, facilitating wound healing, in addition to the growth and invasion of tumor cells.[1] Since proteases are generally classified based on their catalytic mechanisms, cathepsins are subdivided according to their active site amino acids, which confers the catalytic activity, into *cysteine* (cathepsins B, C, F, H, K, L, N, O, S, T, U, W and X), *serine* (cathepsins A and G), and *aspartic* cathepsins (cathepsin D and E).[2]

Over the last decade, cathepsin L had been of great interest due to its numerous functions. It appeared to be critically involved in epidermal homeostasis, regulation of the hair cycle and major histocompatibility complex (MHC) class II-mediated antigen presentation in cortical epithelial cells of the thymus.[2,3] The expression of cathepsin L in the thymus is essential for natural killer T-cell (NKT) development. Surprisingly, cathepsin L-deficient mice were shown to develop epidermal hyperproliferation and periodic hair loss.[4]

Cathepsin L is a lysosomal cysteine protease consisting of a heavy chain of about 25 kDa and a light chain of about 5 kDa derived proteolytically from the same precursor.[5] Several variants of cathepsin L have been described. Some of these differ only in the 5-prime noncoding region.[6,7] Cathepsin L1 is a protein that in humans is encoded by the *CTSL1* gene. Cathepsin L2 is also known as cathepsin V and encoded by the *CTSL2* gene.[8] Increased cathepsin L activity and secretion has been observed in many human cancers. Various reports also suggested that cathepsin L levels could be used as a potential indicator of tumor aggressiveness and metastasis.[9] Increased nuclear cathepsin L expression and activity was found in various cancer cells, suggesting a different mechanism of cellular transformation such as breast cancer, gastric carcinoma, ovarian cancer, bladder cancer, and pancreatic adenocarcinoma.[10]

Higher concentration of cathepsin L in early primary melanomas correlates with poor prognosis and indicate possible early metastatic spread.[11] Cathepsin L was found to be elevated in malignant cells of squamous cell carcinoma. Cathepsin L may promote tumor cell invasion and metastasis by catalyzing degradation of the interstitial matrix and basement membranes, thus allowing cancer cells to invade locally and metastasize to distant sites. Several tumor-forming cell lines are known to over-produce cathepsin L.[12] Endogenous and exogenous proteases such as cathepsins, and proteases derived from microorganisms are important in the desquamation process of the stratum corneum and are able to activate and inactivate defense molecules in human epidermis. Changes in the proteolytic balance of the skin can result in inflammation, which leads to the typical clinical signs of redness, scaling, and itching. Proteases, their inhibitors, and their target proteins, including filaggrin (FLG), protease-activated receptors, and corneodesmosin, contribute to the pathophysiology of inflammation of the skin and highlight their role in common inflammatory skin diseases such as AD, rosacea, and psoriasis.[13]

Atopic dermatitis is a polygenic disease that is heavily influenced by many factors including the genetic, environmental and immunological factors. The cytokine profile in AD skin changes during the course of the disease towards a mixed T helper (Th1/Th2) cytokine profile. Activated Th2 cells play a key role in the pathogenesis of AD.[14] There are two main phases in etiology of AD; the first phase is characterized by the stimulation of Th2 lymphocytes with its cytokine pattern including the up regulation of IL-4, IL-5, and IL-13 and also up regulation immunoglobulin (IgE). The second phase is characterized by the stimulation of Th1 cytokines including the interferon gamma (IFN- γ), and down regulation of IgE.[15] The etiology of LP appears to be complex, and still unclear with interaction between the genetic, immunological, environmental and life style factors. T-cells are the predominant cells in the inflammatory infiltrate. Although the specific antigen of LP is still unclear, the antigen presentation by basal keratinocytes are thought to cause T-cell accumulation in the superficial lamina propria, basement membrane disruption, intra-epithelial T-cell migration, and CD8+ cytotoxic cell (CTL) mediated keratinocytes apoptosis in LP.[16]

There is evidence that an increase in proteinase activity occurs in lichenoid and eczematoid epidermis. Normal epidermis contained abundant inactive precursors (39 kDa) of cathepsin L.[17] The activated mature enzymes hydrolyze FLG and are probably involved in the keratinization process. Therefore, some authors hypothesized that some inactive epidermal cysteine proteases(s) are activated in diseases such as AD and LP which are characterized by abnormal keratinization.[18]

The aim of this work was to study the immunohistochemical expression of cathepsin L in AD and LP in a trial to understand its possible role in their pathogenesis.

Materials and Methods

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The present study was carried out on 30 patients; 15 patients with AD (Group I) and 15 patients with LP (Group II), in addition, to 10 healthy skin specimens served as controls (Group III). They were selected from the Outpatient Clinic of Dermatology and Venereology Department, Tanta University Hospitals from October 2011 up to May 2012.

Patients groups Were classified into:-

Atopic dermatitis patients

(Group I) included 15 patients with AD, diagnosed according to the clinical criteria of Hanifin and Rajaka.[19] The severity of disease was assessed via scoring atopic dermatitis (SCORAD).[20] It gives information on the extent of the affected body, intensity of six clinical signs (erythema, edema/papules, excoriation, oozing/crusts, lichenification and dryness) and subjective symptoms (pruritus and sleep loss during last 3 days). The extent of the affected body, the sites affected by eczema are shaded on a drawing of a body. The rule of nine is used to calculate the affected area (A) as a percentage of the whole body.(Head and neck 9%, upper limbs 9% each, lower limbs 18% each, anterior trunk 18%, back 18%, 1% each for genitals, each palm and the back of each hand.) The total area is (A), which has a possible maximum of 100%. Intensity is graded from 0 to 3 [0: Absent, mild: 1, moderate: 2, severe: 3]. The intensity scores are added together to give (B); maximum 18. The subjective symptoms are graded from 0 to 10 using a visual scale where 0 is no itch (or no sleeplessness) and 10 is the worst imaginable itch (or sleeplessness). These scores are added to give (C); maximum 20. The maximum SCORAD score is 103. The SCORAD index $(0-103) = A/5 (20) + 7B/2 (0-63) + C (0-20)$. It is classified into mild: <25, moderate: ≥25-50 and severe: ≥50.

Lichen planus patients

(Group II) included 15 patients with classical LP. The patients were diagnosed according to the clinical picture and histopathological examination.

Control group

(Group III) included 10 normal healthy skin specimens obtained during the plastic operations.

Inclusion criteria Newly diagnosed patients or old patients who did not receive any systemic or topical treatment for AD or LP in the past 6 weeks, the patients who did not have any other systemic or skin diseases, female patients were not pregnant or receiving any hormonal contraceptives and patients who agreed to join the study and signed a written consent.

The studied persons were subjected to detailed history taking, general and dermatological examination and routine laboratory investigations.

Methods After informed written consent, punch biopsies of 4 mm were taken under local anesthesia from the lesional skin of AD and LP patients. Control biopsies were also obtained from similar sites during the plastic operations. After removal, the biopsies were immediately formalin fixed, and processed routinely and tissue slides were subjected to:- Hematoxylin and eosin (H and E) staining was done to confirm the histopathological changes of AD and LP and immunohistochemical (IHC) staining was done to detect cathepsin L expression using mouse anti-human monoclonal anti- cathepsin L (33/2) antibody ready to use, available from (Santa Cruz Biotechnology, Germany, catalogue number: sc-32320) by overnight exposure in human chamber in dilution 1:100. The secondary antibody was ready to use biotinylated rabbit anti-mouse IgG (Dako, Germany), then streptavidin peroxidase was applied for 10 minutes. The negative control was obtained by substitution of the primary antibody

with phosphate buffer. Cathepsin L positive breast carcinoma specimens were used as a positive control.

Evaluation of immunostaining

The positive investigated cells were scored as:- negative (zero), <25%. Mild (+1): 25-≤50%. Moderate (+2): >50-≤75%. Severe (+3): >75%.[\[21\]](#)

Statistical analysis All data obtained were transferred to the statistical package for the social sciences version 15 (IBM Co., New York, USA) for analysis. Data were summarized using the mean standard deviation (mean ± SD) using student's *t*-test. Comparison between groups were made by using X^2 – test and Fisher exact test for quantitative variables. Statistical significance was determined at a level of $P \leq 0.05$ and highly significance at a level of $P \leq 0.001$.

Results

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Clinical results Atopic dermatitis (Group I)

This group included 15 patients of AD, 7 males (46.7%) and 8 females (53.3%), their ages ranged from 4 to 34 years with a mean ± SD 15.73 ± 9.66 years. The duration of the disease varied from 0.25 to 5 years with a mean ± SD 2.05 ± 1.39 years. Regarding the family history it was positive in 4 patients (26.7%) and negative 11 patients (73.3%) [\[Table 1\]](#). Regarding the severity of AD; the patients were classified according to their SCORAD score into; 8 patients mild/moderate (53.3%) and 7 patients severe (46.7%) [\[Table 2\]](#).

Parameter	Mean	Range	SD
Age (years)	15.73	4-34	9.66
Duration (years)	2.05	0.25-5	1.39
Family history			
Positive	4		
Negative	11		
Gender			
Male	7		
Female	8		

[Table 1](#)

Clinical data of the studied groups regarding age, duration, family history and gender

Severity	No. of patients	Percentage (%)
Mild/moderate	8	53.3
Severe	7	46.7

[Table 2](#)

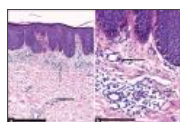
Scoring of atopic dermatitis patients

Lichen planus (Group II)

This group included 15 patients of LP, 7 males (46.7%) and 8 females (53.3%), their ages ranged from 17 to 65 years with a mean ± SD 40.6 ± 15.32 years. The duration of the disease varied from 1 to 8 years with a mean ± SD 4.25 ± 2.14 years. Regarding the family history, it was positive in 2 patients (13.3%) and negative 13 patients (86.7%) [\[Table 1\]](#).

Histopathological results

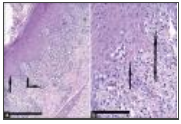
The histopathologic picture of AD is characterized by hyperplasia and hyperkeratosis of the epidermis, spongiosis secondary to intracellular edema in acute lesions, and in chronic lesions, there is moderate to marked hyperplasia of the epidermis, elongation of the rete ridges and prominent hyperkeratosis and areas of parakeratosis, marked infiltrate of lymphocytes, rare monocytes and macrophages is present around the venous plexus in the dermis. [\[Figure 1a and b\]](#).



[Figure 1](#)

(a and b) Atopic dermatitis showing acanthosis [black line] and aggregates of mononuclear cells mainly lymphocytes in the upper dermis [white arrow] mainly perivascular [black arrow] (H and E, ×100 and ×400, scale bar 10 μm)

The histopathologic picture of classical LP is characterized by degeneration of the basal layer of the epidermis and band like lymphocytic infiltrate obscuring the dermoepidermal junction, irregular epidermal hyperplasia forming a characteristic saw-tooth appearance with wedge-shaped hypergranulosis, the basal layer of the epidermis exhibits vacuolar degeneration with typically prominent necrosis of individual keratinocytes, the inflammatory infiltrate is chiefly lymphocytic and forms a dense band in the superficial dermis [\[Figure 2a and b\]](#).



[Figure 2](#)

(a and b) Classic lichen planus showing band like inflammatory infiltrate [arrows] and marked saw tooth acanthosis [arrow] (H and E, $\times 100$ and $\times 400$, scale bar 10 μm)

Immunohistochemical results

Expression of cathepsin L in normal skin was mainly distributed in the entire epidermis which was less than 25% and considered as negative expression [Figure 3]. Cathepsin L was detected in the cytoplasm mostly in diffuse staining pattern or somewhat condensed granular mainly in the lower spinous layers along the elongated rete ridges mainly in AD groups. In the dermis, endothelial cells of blood vessels, infiltrating inflammatory cells (lymphocytes and fibroblasts), all expressed cathepsin L in AD and in LP. In all AD patients, cathepsin L was expressed with different intensities varied from mild in 3 (20%) [Figure 4a, and b], moderate in 5 (33.3%) to severe expression in 7 (46.7%) [Figure 5a and b] [Table 3]. In all LP patients, cathepsin L was expressed with different intensities varied from mild in 8 (53.3%) [Figure 6a and b], moderate in 4 (26.7%) to severe expression in 3 (20%) [Figure 7a and b] [Table 3]. The intensity of cathepsin L expression showed statistically highly significant difference when comparing the two groups and controls ($P = 0.001$), while it showed no statistically significant difference when comparing between Group I and Group II with each other ($P = 0.136$). [Table 3]. The intensity of cathepsin L expression regarding the severity (scoring) of AD patients showed that, it was mild in 2 (25.0%), moderate in 3 (37.5%), severe in 3 (37.5%) in mild/moderate but in severe scoring it was, mild in 1 (14.3%), moderate in 2 (28.6%), marked in 4 (57.1%), ($P = 0.048$). There was statistically significant increase in the intensity of cathepsin L expression in patients with severe AD [Table 4]. [2]



[Figure 3](#)

Normal skin specimens showing negative stain (immunoperoxidase for cathepsin L $\times 100$, scale bar 10 μm)



[Figure 4](#)

(a and b) Atopic dermatitis showing mild (+1) expression for cathepsin L mainly in the lower epidermis [arrow 1], and inflammatory cells (lymphocytes, fibroblasts) [arrows] and endothelial cells in the dermis [arrow 2] (immunoperoxidase for cathepsin ...



[Figure 5](#)

(a and b) Atopic dermatitis showing severe (+3) expression for cathepsin L mainly in the epidermis [star], and in the inflammatory cells (lymphocytes, fibroblasts) [arrows] and endothelial cells in the dermis [arrow] (immunoperoxidase for cathepsin L ...

Group	Intensity	n	%
AD	Mild	3	20
	Moderate	5	33.3
	Severe	7	46.7
LP	Mild	8	53.3
	Moderate	4	26.7
	Severe	3	20

[Table 3](#)

Intensity of cathepsin L expression in the studied groups



[Figure 6](#)

(a and b) Classical lichen planus showing mild (+1) expression for cathepsin L in the epidermis [arrow] and inflammatory cells (lymphocytes) and endothelial cells in the dermis [arrows] (immunoperoxidase for cathepsin L $\times 100$ and $\times 400$, ...



[Figure 7](#)

(a and b) Lichen planus showing severe (+3) expression for cathepsin L in the epidermis [line] and inflammatory cells (lymphocytes) [arrows] and endothelial cells in the dermis [arrow] (immunoperoxidase for cathepsin L

×100 and ×400, ...

Table 4				
Intensity of cathepsin L expression regarding scoring of atopic dermatitis patients				
Intensity of cathepsin L expression	Number of patients	Percentage (%)	Mean	Standard deviation
0	2	10.0	0.00	0.00
1	10	50.0	1.00	0.00
2	8	40.0	2.00	0.00
3	2	10.0	3.00	0.00
4	0	0.0	4.00	0.00
5	0	0.0	5.00	0.00
6	0	0.0	6.00	0.00
7	0	0.0	7.00	0.00
8	0	0.0	8.00	0.00
9	0	0.0	9.00	0.00
10	0	0.0	10.00	0.00

Table 4

Intensity of cathepsin L expression regarding scoring of atopic dermatitis patients

Discussion

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In the current study expression of cathepsin L by IHC was detected in the cytoplasm of normal epidermis as diffuse staining in the entire epidermis. But less than 25% of the investigated cells which was considered negative expression. These results agreed with studies done by Kawada *et al.*, [22] and Plaungwachira *et al.*, [23] as they found cathepsin L expression in normal skin samples. But disagreed with the study done by Bylaite *et al.*, [21] who could not detect cathepsin L in any of normal skin samples by IHC neither the use of higher concentration of the antibodies nor different experimental conditions resulted in any detectable level of expression. On the basis of the importance of cathepsin L for the skin and especially for the hair development, they have further studied the expression of cathepsin L by reverse transcription-polymerase chain reaction (RT-PCR) using RNA isolated from normal skin. They found cathepsin L mRNA to be expressed in all samples analyzed and concluded that cathepsin L is present in normal skin; however, the concentration is below the detection limit. [21]

In the current study, cathepsin L was detected in all lesional skin of AD at mild to severe expression. It was detected in the cytoplasm, mostly in diffuse staining pattern or somewhat condensed granular pattern mainly in the lower spinous layers along the elongated rete ridges. In the dermis, eccrine glands, endothelial cells of blood vessels, and infiltrating inflammatory cells, all expressed cathepsin L.

The present study results confirmed the study done by Bylaite *et al.*, [21] who studied the expression of cathepsin L and its inhibitors huprin by IHC and RT-PCR in inflammatory skin diseases such as AD, psoriasis, lupus erythematosus, and neoplasms including seborrheic keratosis as a benign tumor, actinic keratosis as carcinoma *in situ* and cancers: Squamous cell carcinoma, basal cell carcinoma and malignant melanoma. Additionally infectious folliculitis, a bacterial disease, as well as secondary infected cutaneous lesions, such as acne inversa, pyoderma gangrenosum and chronic leg ulcers. Cathepsin L was expressed approximately in two-thirds of the cases of each disease. Cathepsin L was detected at moderate-to-high level mainly in the lower spinous layers with less expression in the granular and upper spinous layers, the present study agreed with Bylaite *et al.*, as regard AD, however we found cathepsin L expression in all lesional skin of AD with variable degree. The pattern of expression of cathepsin L coincided with them.

Cathepsin L and their inhibitors in the skin has an important role in the pathophysiology of inflammatory diseases, and the course of infectious diseases has revealed that fundamental knowledge of the regulatory mechanisms of proteases and their inhibitors is crucial for understanding of these diverse problems. Regulation of proteolytic enzyme activity is essential for cells and tissues at many levels (activation, compartmentalization, and specific inhibition) because proteolysis at a wrong time and location may have disastrous consequences. [24]

Increased expression of cathepsin L in the inflammatory skin diseases also seems to be of physiological relevance based on the activity cathepsin L to convert the IL-8 precursor into the active form, which stimulates neutrophils and T-lymphocytes to inflamed tissue. IL-8 was found up regulated in epidermis from AD patients. [25] Additionally, cathepsin L is secreted by transformed mouse fibroblasts and converts IL-8 and urokinase-type plasminogen activator into the active form which cleave plasminogen into plasmin which is resistant to inactivation, as it protected from endogenous inhibitors. [26]

The plasminogen system in the epidermis is thought to be the major protease activity involved in the delay of barrier recovery. Repeated barrier disruption with surfactants induces epidermal hyperplasia together with increases in plasmin activity, and thought to lead to dry skin as in AD. [27,28] Cysteine proteases can also mediate pro-inflammatory effects via the proteinase-activated receptor-2 (PAR-2), one of the four members of a new subfamily of G-protein receptors known to be highly expressed on epidermal keratinocytes and dermal endothelial cells. These cell populations respond to PAR-2 signaling with hyperproliferation and enhanced expression of proinflammatory cytokines and chemokines. [29]

Cornification requires a massive activation of epidermal proteases, although for most of these, their precise role

remains elusive. Cysteine- and serine-protease inhibitors are abundantly expressed in the epidermis, suggesting an important role in the control of protease activity. Extracellular proteases are particularly abundant in the cornified envelope and are involved in the control of desquamation. Corneodesmosomal proteins that are degraded during desquamation include desmoglein-1, desmocollin-1, plakoglobin and corneodesmosin.[30,31] The intensity of cathepsin L expression was statistically significant increased in severe AD (SCORAD), it could be a useful marker for assessing AD severity.

Regarding LP, in the current study, cathepsin L was expressed in all cases at variable degree from mild to severe expression, mild was found in 53.3%, moderate in 26.7% and severe in 20%. Cathepsin L was detected as a cytoplasmic expression mostly in diffuse staining pattern. In the dermis, infiltrating inflammatory cells expressed cathepsin L. Up to our knowledge there was only one study done by Bylaite *et al.*,[21] and they did not find cathepsin L expression in LP lesional skin, but they found expression of its inhibitors (huprin). The same study suggested that, dysregulation of cathepsin L/huprin system plays a role in the pathogenesis of LP.

The exact cause of elevation of cathepsin L level in LP and its mechanism of action is still unknown, it could be suggested that breakdown of the regulation of cathepsin L expression and its inhibitors in the epidermis in LP results in excessive cathepsin L production. It is also suggested that, since cathepsin L levels are elevated in the epidermis of the patients with LP, cathepsin L is considered an important lysosomal enzyme which can hydrolyse the tight junction of corneodesmosomal adhesion proteins in the epidermis, where antigen presentation plays an important role in the pathogenesis of LP.[32] Cathepsin L plays an important role in MHC-11 antigen presentation.[3]

Cathepsin L, under physiologic conditions, is localized intralysosomally. In response to certain signals they are released from the lysosomes into the cytoplasm where they trigger apoptotic cell death via various pathways, including the activation of caspases or the release of proapoptotic factors from the mitochondria.[33] The predominance of activated T lymphocytes in dermoepidermal inflammatory infiltrate in LP was found to be combined with local and systemic release of various cytokines (TNF- α). TNF- α is expressed on the surface of most CTL and may induce apoptosis, contributing to the cytotoxic effects on target cells in vivo. Apoptosis is considered an important mechanism of cell death in LP.[34] Lysosomal cysteine cathepsins also play an important role in TNF- α -induced cell death. Cathepsin L dysregulation, impairs the desquamation with subsequent dryness and hyper proliferation in the epidermis.[33] It enhances the expression of pro inflammatory cytokines and chemokines and thus perpetuating the immunological reaction.[35]

Conclusion

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This study showed significantly increase in the expression of cathepsin L in AD and LP, this suggests that cathepsin L may have a possible role in the pathogenesis of AD and LP. It could be a useful marker for assessing AD severity. Additional studies that might be of clinical relevance will further elucidate the physiological role this protein.

What is new?

The localization of the protease cathepsin L by IHC in LP and using it as a useful marker for assessing AD severity was first time described by this study.

Footnotes

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Source of support: Nil

Conflict of Interest: Nil.

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