Decreased Chymase Activity is Associated with Increased Levels of Protease Inhibitors in Mast Cells of Psoriatic Lesions

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INVESTIGATIVE REPORTS

Psoriasis is a chronic inflammatory skin disease and its aetiology and pathogenesis are controversial. Mast cells have been observed in increased numbers in lesional psoriatic skin, where they are typically located beneath the epidermis (1–3). Recently, tryptase-positive mast cells have also been reported in increased numbers in non-involved skin of patients with psoriasis. They also associate with duodenal intraepithelial lymphocytes and mast cells (4). Degranulated mast cells and endothelial swelling in postcapillary venules are among the earliest morphological observations in the evolving psoriatic lesion (5–7), suggesting a role for mast cells both in the developing and mature psoriatic lesions.

Mast cells contain large amounts of the powerful serine proteinases, tryptase and chymase, of which only chymase can be inactivated by serum protease inhibitors. In this study, 20 patients with psoriasis and a control group of 13 with atopic dermatitis were biopsied for lesional and non-lesional skin specimens. The presence of chymase inhibitor τ1-proteinase inhibitor (τ1-PI), τ1-antichymotrypsin (τ1-AC), τ2-macroglubulin (τ2-MG) and C1-esterase inhibitor (C1-Inh) immunoreactivity in mast cells was verified using the sequential double-staining method. Tryptase- and chymase-positive mast cells were stained enzyme-histochemically. Tryptase-positive mast cells were increased in number in the upper dermis of the psoriatic lesion compared with lesion-free psoriatic skin (308 ± 109 vs. 100 ± 29 cells/mm2, respectively, mean ± SD, p < 0.0005, t-test) while the percentage of mast cells showing chymase activity was decreased (76.8 ± 22.1% vs. 28.6 ± 14.4%, p < 0.0005). These findings are consistent with our previous ones. In contrast to the decreased percentage of chymase-positive mast cells, a novel finding was that the percentages of τ1-AC (86.9 ± 7.2% vs. 59.5 ± 12.6%, p < 0.0005), τ1-PI (72.2 ± 14.9% vs. 33.4 ± 18.6%, p < 0.0005) and τ2-MG+ (16.8 ± 7.0% vs. 6.2 ± 3.5%, p < 0.002) mast cells were significantly higher in the psoriatic lesion with the exception of the percentage of C1-Inh+ mast cells (13.7 ± 10.0% vs. 11.0 ± 6.1%, p < 0.7). The localization of these inhibitors in mast cells is not a characteristic feature of psoriasis, since mast cells in atopic dermatitis skin also showed immunoreactivity though in slightly lower percentages. Previously, we have shown that MC TC (tryptase-, chymase+ ) mast cells increase in number in the psoriatic lesion but chymase becomes inactive. The results of this study show again the decreased chymase activity, which could be due to increased levels of its inhibitors (τ1-AC, τ1-PI and τ2-MG) in the same mast cells. Thus, active tryptase could promote inflammation but chymase seems not to be an important mediator in the pathomechanism of psoriasis. Key words: mast cell; protease inhibitor; tryptase; chymase; psoriasis.

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Table I. Protease inhibitors and proteinase activity in mast cells of psoriatic skin. Tryptase-positive cells reflect the total mast cell count (MC and MC
count). The staining intensity of protease inhibitors in mast cells was evaluated as weak, moderate or intense.

<table>
<thead>
<tr>
<th>Mast cell staining</th>
<th>Lesional skin</th>
<th>Non-lesional skin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cells/mm²</td>
<td>% (of total cells)</td>
</tr>
<tr>
<td>Tryptase activity (n = 20)</td>
<td>308 ± 109ᵇ</td>
<td>28.6 ± 14.4ᵇ</td>
</tr>
<tr>
<td>Chymase activity (n = 20)</td>
<td>89 ± 49</td>
<td>50.9 ± 17.7ᵇ</td>
</tr>
<tr>
<td>α1-Proteinase inhibitor (n = 20)</td>
<td>87.8 ± 9.5ᵇ</td>
<td>94.7 ± 4.0ᵇ</td>
</tr>
<tr>
<td>At least weak staining</td>
<td>72.2 ± 14.9ᵇ</td>
<td>86.9 ± 7.2ᵇ</td>
</tr>
<tr>
<td>At least moderate staining</td>
<td>16.8 ± 7.0ᵃ</td>
<td>13.7 ± 10.0</td>
</tr>
<tr>
<td>At least strong staining</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The values are expressed as mean ± SD.
ᵃ p < 0.002;ᵇ p < 0.0005 (paired t-test, lesional vs. non-lesional skin).

30). Psoriatic patients with α1-PI deficiency (MZ phenotype) even show more and larger basal keratinocyte herniations through the gaps in the basal lamina than controls (31). Since chymase and tryptase are major secretory proteins in mast cell granules both with potent biological activities we have investigated and extended our preliminary observations on the localization of α1-proteinase inhibitor and α1-antichymotrypsin in mast cells (15) and now performed a quantitative analysis in a new biopsy series to show alterations in α1-proteinase inhibitor and α1-antichymotrypsin, but also, in this study, alterations in C1-esterase inhibitor and α2-macroglobulin. For this, we took skin biopsies from patients with psoriasis vulgaris and atopic dermatitis chosen as the control disease for psoriasis. No previous reports are available to show protease inhibitors in mast cells of atopic dermatitis lesions. Enzyme- and immunohistochemistry were applied to demonstrate trypase and chymase enzyme activity as well as different protease inhibitors in mast cells using a method described previously (15).

MATERIALS AND METHODS

Chemicals

The source for chemicals and materials has been reported in our previous study (15). The substrates (Z-Gly-Pro-Arg-4-methoxy-2-naphthylamide and Suc-Val-Pro-Phe-MNA) for enzyme-histochemistry were purchased from Bachem (Bubendorf, Switzerland). Rabbit antibodies against α1-proteinase inhibitor (α1-PI), α1-antichymotrypsin (α1-AC) and α2-macroglobulin (α2-MG) were obtained from Dako (Glostrup, Denmark), and a rabbit antibody against complement C1-esterase inhibitor (C1-Inh) from Calbiochem (La Jolla, CA, USA).

Patients and skin and blood samples

The study included 20 subjects with psoriasis vulgaris (11 males and 9 females, age range 23–69 years, mean age 51 years). All patients were biopsied from untreated skin sites for a psoriatic lesion and a healthy-looking skin sample (at least 2 cm away from the psoriatic plaque). Only patients without any systemic or effective local treatments for at least 1 month prior to biopsy were accepted. The clinical condition of the patients was variable from occasional to widely spread psoriatic plaques (Psoriasis Area and Severity Index, PASI, 1.6–20.5, mean 6.7).

A total of 13 patients with atopic dermatitis were selected according to the diagnostic criteria of Hanifin & Rajka (32) and they served as the control group. These patients had either acute or subacute exacerbation of the skin rash, and each of them was biopsied for lesional and non-lesional skin samples.

Skin biopsies were taken after local anaesthesia (1% lidocaine with adrenaline) in the Department of Dermatology, Kuopio University Hospital. After removal, the specimens were immediately embedded in OCT compound (Miles Scientific, Naperville, IL, USA) and frozen in isopentane cooled with a mixture of absolute ethanol and dry ice. Blood samples were drawn from antecubital veins using routine techniques. Serum α1-PI concentration was measured using immunnoassay and its isotypes with isoelectric focusing (29–31). The methods used were approved by the Ethics Committee of Kuopio University Hospital, Kuopio, Finland.

Enzyme-histochemical staining methods for trypase and chymase

Cryosections 4 µm thick were cut on poly-L-lysine coated slides which were stored at −20 °C. Prior to staining, the sections were fixed in 0.6% formaldehyde and 0.5% acetic acid, pH 7.2, for 10 min. Mast cell trypase was stained with 1 mM Z-Gly-Pro-Arg-MNA as the selective and sensitive substrate as described previously (9, 15). Mono Mac 6 and U937 monocytic cell lines show no staining but KU812 basophilic cell line exhibits less than 0.5% of the cells as trypase-positive (33). MOLT-4 T lymphoblasts show no staining either (unpublished). Mast cell chymase was stained with 1 mM Suc-Val-Pro-Phe-MNA as the specific substrate (3, 15).

Immunohistochemical staining methods

For immunohistochemical staining, the skin sections were fixed in cold acetone for 15 min. The bound polyclonal anti-α1-PI (0.55 µg/ml), anti-α1-AC (3.4 µg/ml), anti-C1-Inh (1:500), and anti-α2-MG (0.72 µg/ml) antibodies on skin sections were visualized with Vectastain Elite ABC kit (Vector Laboratories, Burlingame, CA, USA) as described previously (15). Non-specific staining was ruled out by using 100 µg/ml purified goat IgG (Sigma, St. Louis, MO, USA) dissolved in 1% bovine serum albumin and phosphate-buffered saline as the blocking reagent and by using unrelated rabbit polyclonal antibodies in higher concentrations than the specific antibodies.

Sequential double-staining method

The immunoreactivity of protease inhibitors in mast cells was shown with the sequential double-staining method by first demonstrating mast cell trypase with Z-Gly-Pro-Arg-MNA (15, 33). Thereafter, at least 6 adjacent photographs from the epidermal border to approximately 0.4 mm down the dermis were taken at random sites. Subsequently, the red azo dye was dissolved away by an overnight...
incubation in 15% Tween 20. Then, the same sections were fixed in acetone, stained immunohistochemically and re-photographed at exactly the same site as the previous pictures. The control skin sections were processed identically but with unrelated rabbit antibodies. The intensity of the staining reaction product in mast cells was graded as weak staining (very faint but clearly identifiable staining product), moderate staining, and intense staining.

Counting of mast cells and statistics

Mast cells showing tryptase or chymase activity were counted, as described (15), in an area of 1.2 mm wide × 0.4 mm deep immediately beneath the papillary dermis. The area of lesional papillary dermis was measured with the Quantimet image analysis system (Leica, Nussloch, Germany), and the mast cells in papillary dermis were then counted separately (3, 15). The number and the percentage of α1-PI+, α1-AC+, CI-Inh+ and α2-MG+ mast cells was counted by comparing the photographs simultaneously as described previously (33). Student’s t-test was used for statistical analysis.

RESULTS

Tryptase and chymase in psoriatic skin

The density of tryptase+ and chymase+ mast cells in the upper dermis of non-lesional psoriatic skin was 100 ± 29 and 75 ± 28 cells/mm², respectively (Table I). Since both tryptase and chymase enzyme activities co-exist in the same mast cells, as shown previously by a sequential double-staining method (3), on an average 76.8 ± 22.1% of the tryptase+ cells displayed chymase activity.

As shown in Table I, tryptase+ cells were significantly increased in number by 3-fold (p < 0.0005) in the psoriatic lesion compared with non-lesional psoriatic skin. In contrast, lesional skin mast cells with chymase activity exhibited only weak staining intensity in the uppermost dermis, but clear staining in the deeper part of dermis and chymase+ cell count did not differ significantly from that observed in non-lesional skin (89 ± 49 vs. 75 ± 28 cells/mm²) (for a figure showing chymase+ mast cells)
mase activity in the psoriatic lesion see our previous study (3). However, the percentage of chymase mast cells in lesional skin was significantly reduced to one third ($p < 0.0005$). In general, these results agree with our previous ones in 2 other series of psoriasis specimens (3, 15). The concern that chymase could be inactivated by soluble endogenous protease inhibitors during the 30-min staining reaction is not likely since inclusion of pure $\alpha_1$-PI or $\alpha_1$-AC in the staining solution could not markedly interfere with the chymase staining in non-lesional skin under experimental conditions nor could the prolonged fixation of skin sections yield any additional chymase activity in the papillary dermis of lesional skin (15).

Protease inhibitors in mast cells of psoriatic skin

The presence of various protease inhibitors in mast cells was quantified, and the results are summarized in Table I. Immunoreactivity for $\alpha_1$-PI, $\alpha_1$-AC, $\alpha_2$-MG and Cl-inh could be found in mast cells in both lesion-free and lesional skin specimens (Fig. 1 and 2). The localization of $\alpha_1$-PI and $\alpha_1$-AC in mast cells was also confirmed by staining in reverse order, i.e. the protease inhibitors were first stained immunohistochemically followed by tryptase staining (Fig. 3). In addition, 2 formalin-fixed and paraffin-embedded lesional psoriatic skin specimens were processed for immunohistochemical staining of $\alpha_1$-PI and $\alpha_1$-AC after treatment of the skin sections with 5 mg/ml pepsin for 40 min to increase antibody penetration and without previous tryptase staining. The staining of these inhibitors showed numerous dendritic mast-like cells in the dermis (not shown) with a similar staining pattern as on the cryosections illustrated in Fig. 3a. These control stainings strongly suggest that the immunoreactivity of protease inhibitors in mast cells is not an artefact due to tissue processing.

Fig. 3. A section of lesional psoriatic skin stained with (a) polyclonal anti-$\alpha_1$-proteinase inhibitor antibody. After photographing, the same section was stained with (b) Z-Gly-Pro-Arg-MNA as the substrate and Fast Garnet GBC as the chromogen. Numerous $\alpha_1$-proteinase inhibitor-positive cells exhibit tryptase activity (bright red stain). Magnification × 380.

Fig. 4. Association between mast cells showing chymase activity with those displaying (a) $\alpha_1$-antichymotrypsin immunoreactivity ($r = -0.61$, $p = 0.004$, Spearman correlation test), and with those displaying (b) $\alpha_1$-proteinase inhibitor immunoreactivity ($p = 0.441$ and $r = -0.19$, when the single deviating value is omitted) in the upper dermis of the psoriatic lesion in 20 subjects with psoriasis vulgaris. The percentages were calculated in relation to tryptase-positive mast cells.
There were also numerous cells other than mast cells with immunoreactivity for \( \alpha_1 \)-PI and \( \alpha_1 \)-AC as found previously (15). These cells are probably macrophages that are known to be positive for these inhibitors. \( \alpha_1 \)-PI and \( \alpha_1 \)-AC exhibited high percentages even in non-lesional skin (33.4\% ± 18.6\% and 59.5\% ± 12.6\%, respectively) (Fig. 1). A relatively low proportion of the mast cells in non-lesional skin were positive for \( \alpha_2 \)-MG and Cl-inh (6.2\% ± 5.5\% and 11.0\% ± 6.1\%, respectively).

The percentage of \( \alpha_1 \)-PI, \( \alpha_1 \)-AC, and \( \alpha_2 \)-MG mast cells, but not Cl-inh, was significantly increased in the psoriatic lesion compared with non-lesional controls. Furthermore, the mast cells appeared to show more intense staining for \( \alpha_1 \)-PI and \( \alpha_1 \)-AC in the psoriatic lesion (Fig. 2) since relatively higher proportion of the mast cells were at least moderately stained (Table I). As much as 86.9\% ± 7.2\% and 72.2\% ± 14.9\% of the mast cells were positive for \( \alpha_1 \)-AC and \( \alpha_1 \)-PI, respectively, but only 16.8\% ± 7.0\% for \( \alpha_2 \)-MG, in the psoriatic lesion. The increasing percentage of \( \alpha_1 \)-AC but not that of \( \alpha_1 \)-PI immunoreactivity in mast cells is significantly associated with a decreasing percentage of chymase activity in individual patients (Fig. 4a,b).

Two patients out of 20 showed MZ \( \alpha_1 \)-PI phenotype in serum with an \( \alpha_1 \)-PI concentration of 1.5 g/l and 1.5 g/l, but the remaining 18 patients exhibited MM phenotype with an \( \alpha_1 \)-PI concentration of 2.0 ± 0.3 g/l (mean ± SD). In addition, these MZ phenotype patients showed 95.6\% and 80.2\% of the lesional skin mast cells as \( \alpha_1 \)-PI positive (at least moderate staining intensity), which are slightly higher percentages than the mean (72.2\%).

**Protease inhibitors in mast cells of atopic dermatitis skin**

To determine whether the expression of protease inhibitors in mast cells is characteristic for psoriatic skin, lesional and lesion-free skin specimens from patients with atopic dermatitis were double-stained as described above. Lesional atopic skin showed 55.5\% ± 16.4\% of the mast cells as \( \alpha_1 \)-AC positive with at least moderate staining intensity, which is significantly higher than the percentage found in non-lesional skin (40.2\% ± 15.3\%) (\( p < 0.03, n = 13 \)). However, no significant increases in the percentages of Cl-inh and \( \alpha_2 \)-MG mast cells were observed from non-lesional to lesional skin (from 5.5\% ± 7.4\% to 9.7\% ± 6.8\%, \( p < 0.3, n = 5 \); and from 5.6\% ± 7.1\% to 14.3\% ± 12.1\%, \( p < 0.11, n = 6 \), respectively).

**DISCUSSION**

Several previous reports have shown that human cutaneous mast cells display immunoreactivity for \( \alpha_1 \)-PI and \( \alpha_1 \)-AC (15, 34–36). In fact, the cytoplasmic staining of these inhibitors in mast cells has been shown to be intense and granular in formalin-fixed and paraffin-embedded skin specimens (35, 36), supporting the assumption that mast cells have the capability to synthesize and store these substances in their secretory granules. However, serum contains high levels of \( \alpha_1 \)-PI and \( \alpha_1 \)-AC which could diffuse from circulation and bind to their counterpart proteinases exposed to the extracellular environment after mast cell degranulation.

In our previous studies, we have used the double-staining method to demonstrate both tryptase enzyme activity and immunoreactivity in the same mast cells of normal, mastocytoma and psoriatic skin (2, 9, 15). In every case, tryptase protein without enzyme activity has not been observed, which is in good agreement with the findings that no known physiological inhibitors for tryptase have been found. Serum protease inhibitors do not inhibit tryptase nor can tryptase degrade them (18, 37). However, in inflamed herpes zoster skin we have observed tryptase immunoreactivity without apparent enzyme activity but the cellular origin of this tryptase protein is obscure (33). Tryptase is considered a powerful mediator with a prolonged action time since it is bound to large heparin proteoglycan complexes that diffuse slowly from the site of mast cell activation (18). Chymase, on the other hand, is susceptible to inactivation by \( \alpha_1 \)-PI and \( \alpha_1 \)-AC but it can also degrade these inhibitors efficiently (17, 38). \( \alpha_1 \)-PI can be inactivated by other enzymes, too, including neutrophil myeloperoxidase (39), cathepsin L (40), matrix metalloproteinases, such as matrilysin, gelatinase, collagenase and stromelysin (41), and *Staphylococcus aureus* serine proteinase (42). Tryptase could be increased \( \alpha_1 \)-PI inactivation indirectly by activating first matrix metalloproteinases (43, 44). Also Cl-Inh and \( \alpha_1 \)-AC are susceptible to inactivation by several different proteolytic enzymes (45).

In the present study, tryptase\(^{\dagger}\) mast cells were significantly increased in number, but the percentage of mast cells showing chymase activity was greatly reduced in the psoriatic lesion, which is in agreement with our previous work (3, 15). We have also counted tryptase\(^{\dagger}\) and chymase\(^{\dagger}\) mast cells during prick-test wheal reactions in healthy-looking skin and found a deeper reduction in chymase\(^{\dagger}\) cells than in tryptase\(^{\dagger}\) cells only 30 min after the allergen challenge (unpublished). In contrast to chymase, the percentage of mast cells containing \( \alpha_1 \)-PI, \( \alpha_1 \)-AC, and \( \alpha_2 \)-MG was significantly increased in the psoriatic lesion compared with lesion-free skin. No significant increase could be observed in C1-Inh-positive mast cells. This apparent inactivation of chymase together with simultaneous upregulation of its inhibitors in mast cells suggests that these protease inhibitors have inhibited chymase. Although chymase is inhibited relatively slowly by \( \alpha_1 \)-PI and \( \alpha_1 \)-AC compared with the inhibition rate of cathepsin G and elastase (17), chymase could be exposed to increased concentrations of \( \alpha_1 \)-PI and \( \alpha_1 \)-AC in the psoriatic lesion where mast cells are in the stage of degranulation (5, 6) and functionally hyperreactive (46). Thus, these inhibitors could take the control over released chymase at the physiological pH of extracellular environment. The previous report by Schechter et al. (17) has shown that \( \alpha_1 \)-PI and \( \alpha_1 \)-AC account for the major inhibitory capacity of plasma on human chymase, whereas only 20\% of the chymase inactivation could be explained with \( \alpha_2 \)-MG. Furthermore, \( \alpha_1 \)-AC is a more potent inhibitor of chymase than \( \alpha_1 \)-PI (17). This well agrees with the present finding that \( \alpha_1 \)-AC showed highest percentages in mast cells of both lesional and non-lesional psoriatic skin (Table I), and there is a significant inverse correlation between \( \alpha_1 \)-AC and chymase-positive cells (Fig. 4). However, the expression of these protease inhibitors in mast cells is not a unique feature of psoriasis since mast cells in atopic dermatitis skin, mastocytoma skin (34–36) and herpes zoster skin (33) can also express these inhibitors.

The biological function of chymase is still obscure, though several reports have been published in this field. Chymase is supposed to modulate the cytokine cascade in psoriasis since it can efficiently activate pro-interleukin-1β to interleukin-1β (47). The increase in non-functional interleukin-1β in psoriasis (48) could, in part, be due to the inactivation of chymase. Other
possible functions of chymase are its degradative effects on neuropeptides substance P (SP) and vasoactive intestinal peptide (VIP) (49), and on bradykinin (50). SP and VIP can substantially induce degranulation of skin mast cells (51). On the other hand, increased neurofilament-, SP- and VIP-positive sensory nerve fibres and their morphological contacts with mast cells have been found in the psoriatic lesion (52). The apparent inactivation of chymase by protease inhibitors observed on skin sections could result in the failure of controlling the SP-mediated neurogenic inflammation in psoriasis. This hypothesis is supported by the finding that chymase can degrade SP, whereas tryptase cannot (49, 53).

The high expression of $\alpha_1$-AC and $\alpha_1$-PI, but low expression of $\alpha_2$-MG and C1-Inh, in mast cells of lesional and even lesion-free psoriatic skin suggests that mast cells attempt to control their proteolytic enzymes, chymase and a cathepsin G-like proteinase, by themselves. Mast cells even exhibited those protease inhibitors which can efficiently inhibit these chymotryptic enzymes (17, 38). The other well-known target of $\alpha_1$-PI is neutrophil elastase in psoriatic skin (26, 27). However, whether mast cells can synthesize these inhibitors or whether they are derived from dilated capillaries remains to be examined, but it is possible that both mechanisms are working during inflammation.

In cutaneous inflammatory reactions, numerous proteases and their inhibitors are functioning simultaneously. While protease inhibitors attempt to control the destructive attack of proteolytic enzymes, these proteases try to escape by destroying their inactivators. In the psoriatic lesion, like also in herpes zoster (33) and atopic dermatitis skin (54), $\alpha_1$-AC and $\alpha_1$-PI probably have taken control over chymase. This suggests that chymase can have suppressive effects on the inflammation in psoriasis whereas tryptase can promote it.

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