Matrix metalloproteinase-7 could be a predictor for acute inflammation in psoriatic patients

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Abstract

Purpose

The pathogenesis of psoriasis is characterized by a disruption of extracellular matrix (ECM) in which matrix metalloproteinases (MMPs) participate actively. We aimed to determine MMP-7 level and its association with the inflammatory response in order to determine its usefulness as a biomarker for psoriasis prediction. We also aimed to determine its distribution in uninvolved and involved psoriatic skin to evaluate the probable role of MMP-7 in psoriasis pathogenesis.

Materials and methods

We recruited 108 psoriatic patients and 133 healthy controls. MMP-7, tissue inhibitors of metalloproteinases (TIMPs) and interleukin-6 (IL-6) levels were measured by Enzyme-Linked Immunosorbent Assay (ELISA) assay. MMP-7 expression was detected by Immunohistochemistry (IHC) study.

Results

ECM turnover and inflammatory biomarker levels were significantly higher in psoriatic patients. MMP-7 revealed to be independently associated to psoriasis even after adjustment for different models. The area under the curve (AUC) of MMP-7 and inflammation Z-score were similar. MMP-7 was positively correlated with IL-6 and inflammation Z-score. Psoriasis severity (PASI) was correlated significantly with IL-6 ($p = 0.007$). The MMP-7 expression was detected in the epidermis of involved and uninvolved psoriatic skin. In involved skin, MMP-7 was expressed by basal and mostly suprabasal keratinocytes. In uninvolved skin, expression of MMP-7 was restricted to basal keratinocytes.

Conclusion

MMP-7 is independently associated to psoriasis disease and to inflammatory response which make it a potential biomarker for this dermatosis.

Introduction

Psoriasis is a chronic inflammatory skin disease with a possible nail and joint involvement and with impaired quality of life. The worldwide prevalence of psoriasis varies from 0.15% to 11.43% in adults [1]. Pathogenesis of psoriasis involves all major physiological processes in which extracellular matrix (ECM) actively participates [2]. Indeed, ECM is the major component of cutaneous tissue [3]. The quality of this ECM depends on a balance between the synthesis of macromolecules and their degradation by proteolytic agents including metalloproteinases (MMP) [4]. MMPs have the ability to degrade all the components of both ECM and basement membrane (BM) [5]. Proteolytic activity of MMPs is inhibited by their

specific inhibitors called tissue inhibitors of metalloproteinases (TIMPs) which bind to MMPs in a 1:1 stoichiometric ratio. The disequilibrium between MMPs and TIMPs leads to pathological conditions [6]. During the disease eruption, MMPs expression is modulated and this modulation is associated to the disease severity. In fact, MMPs are involved in the alteration of intracellular contacts leading to epidermis structural changes, in tissue remodeling, cell migration, angiogenesis and inflammation [7]. Additionally, the inflammatory response is normally accompanied by an increase in expression of MMPs [8]. MMPs and their TIMPs were considered as objective and potential biomarkers for psoriasis detection and severity [9].

In psoriasis were extensively studied the two gelatinases (MMP-2 and MMP-9), stromelysin-1 (MMP-3) and their specific inhibitors TIMPs for describe the role of this markers in the pathogenesis of psoriasis [9]. MMP-2 and MMP-9 play an important role in early progression psoriatic lesion [10]. In fact, MMP-2 was reported to be upregulated in psoriatic skin compared to healthy skin. Sidhom et al were found increased expression of MMP-2 in psoriatic epidermis, epidermal appendages and dermis [11]. This enzyme was detected in both involved and uninvolved skin [12]. MMP-9 was expressed by psoriatic epidermis in skin lesions, fibroblasts and immune cells [7]. However MMP-9 increased level was associated with a decreased psoriatic keratinocyte growth [13]. Furthermore, published results have reported an upregulation of MMP-9 gene in psoriatic patients [14], [15]. MMP-3 has been found in the epidermal areas with high hyperproliferation activity in lesional psoriatic skin [16]. In addition, this protein is used to differentiate psoriasis from psoriatic Arthritis [17]. MMP-3 may aggravate the inflammatory status by activating another MMP named MMP-7 which activated MMP-2 and MMP-9 [18], [19]. Therefore, according to the bibliographic data, MMP-7 seems to be an activator of other proteins such as both gelatinases [19], [20]. Moreover, MMP-7 is able to induce epithelial-to-mesenchymal transition process in cancer diseases [21], [22]. This phenomena is responsible for changes seen in psoriatic epidermal keratinocytes [23]. MMP-7 is involved in the pathogenesis of psoriasis [7] despite the fact that its clinical significance is not fully elucidated in this disease. In fact, MMP-7 belongs to the matrilysin family and lacks the hemopexin-like domain compared to other MMPs. This enzyme is essential for reepithelialization during wound healing [24]. Aberrant expression of MMP-7 inhibits wound healing and is associated with malignant progression in chronic wounds [25], [26]. Chronic inflammatory autoimmune diseases are linked to the MMP-7 expression including systemic lupus erythematosus and its level is correlated with the disease activity [27]. Few studies have investigated the role of MMP-7 in psoriasis. The present study firstly aimed to determine MMP-7 circulating level and its association with the inflammatory response with a special focus to discuss its usefulness as a biomarker for the prediction of the disease. Our second objective was to determine its distribution in uninvolved and involved skin in psoriatic patients to evaluate the probable role of this metalloproteinase in psoriasis pathogenesis.

Section snippets

Study population

The study was approved by the Ethics Committee of Rabta Hospital and informed consent was obtained from all participants to this study. This work was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.
One hundred and eight patients with psoriasis plaques were included in the department of dermatology in La Rabta Hospital University. Exclusion criteria were as follows: the presence of other forms of

Results
Clinical characteristics of each group were summarized in Table 1. There was no significant difference in gender, age and body mass index (BMI) between psoriatic patients and healthy controls (Table 1).

Discussion
The present study aimed to identify a useful biomarker in peripheral blood and tissues of psoriasis patients to evaluate association of this biomarker with psoriasis pathogenesis and its relationship with inflammatory response.
Our results showed that the MMP-7 level increased significantly in psoriatic patients' plasma. In the blood of psoriatic patients, MMP-7 is not secreted in significant quantities by unstimulated myeloid-derived suppressor cells [30]. We found an aberrant expression of

Conclusion
In conclusion, the overproduction of MMP-7 in plasma and tissue of psoriatic patient indicate the utility of MMP-7 in psoriasis detection. In addition, its relationship with the inflammation Z-score and IL-6 shows that MMP-7 seems to present pro-inflammatory activities by inducing macrophages and stimulating skin local inflammatory response. This response leads to tissue damage and constitutive elevation in systemic inflammation. Despite the fact that a further research is needed, the MMP-7

Limitations
First, it is necessary to increase the number of samples, this could provide additional insights about the relationship between MMP-7 and psoriasis severity. In addition, we didn't examine the normal skin in order to compare it with the involved and uninvolved psoriatic skin.

Declaration of Competing Interest
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References (43)

A. Mezentsev *et al.*
Matrix metalloproteinases and their role in psoriasis
Gene.
(2014)
A.M. Manicone *et al.*
Matrix metalloproteinases as modulators of inflammation
Semin. Cell. Dev. Biol.
(2008)
R. Fleischmajer *et al.*
Basement membrane alterations in psoriasis are accompanied by epidermal overexpression of MMP-2 and its inhibitor TIMP-2
J. Invest. Dermatol.
(2000)
N. Buisson-Legendre *et al.*
Relationship Between Cell-Associated Matrix Metalloproteinase 9 and Psoriatic Keratinocyte Growth
J. Invest. Dermatol.
(2000)
C.L. Wilson *et al.*
Matrilysin: an epithelial matrix metalloproteinase with potentially novel functions
Int. J. Biochem. Cell. Biol.
(1996)
T. Elango *et al.*
Serum interleukin-6 levels in response to methotrexate treatment in psoriatic patients
Clin. Chim. Acta.
(2012)
R.E. Vandenbroucke *et al.*
Pro-inflammatory effects of matrix metalloproteinase 7 in acute inflammation
Mucosal. Immunol.