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Review

Matrix metalloproteinases and their role in psoriasis

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ABSTRACT

This review summarizes the contribution of matrix metalloproteinases to the pathogenesis of psoriasis. In psoriasis, matrix metalloproteinases are involved in the structural changes of the epidermis *via* the modification of intracellular contacts and the composition of the extracellular matrix, promoting angiogenesis in the dermal blood vessels and the infiltration of immune cells. Moreover, some matrix metalloproteinases become differentially expressed during the disease eruption and their expression correlates with the clinical score. A separate section of the review is dedicated to the pharmacological approaches that are used to control matrix metalloproteinases, such as oral metalloproteinase inhibitors, such as azasugars and phosphonamides.

The aim of this manuscript is to assess the role of matrix metalloproteinases in the physiological processes that accompany the disease. Moreover, it is especially important to evaluate progress in this field and characterize recently appeared medicines. Because any experimental drugs that target matrix metalloproteinases are involved in active clinical trials, this manuscript also reviews the latest experimental data regarding distribution and expression of matrix metalloproteinases in healthy skin and lesional skin. Therefore, the performed analysis highlights potential problems associated with the use of metalloproteinase inhibitors in clinical studies and suggests simple and easy understandable criteria that future innovative metalloproteinase inhibitors shall satisfy.

Contents

Abbreviations: MMPs, matrix metalloproteinases; MMPI, matrix metalloproteinases inhibitors; ECM, extracellular matrix; TIMPs, tissue inhibitor of metalloproteinase; BM, basal membrane; PBMC, peripheral blood mononuclear cells; FBAT, family-based association test; HB-EGF, heparin-binding epidermal growth factor; HB-GEF, heparin -binding EGF-like growth factor; uPAR, urokinase receptor.

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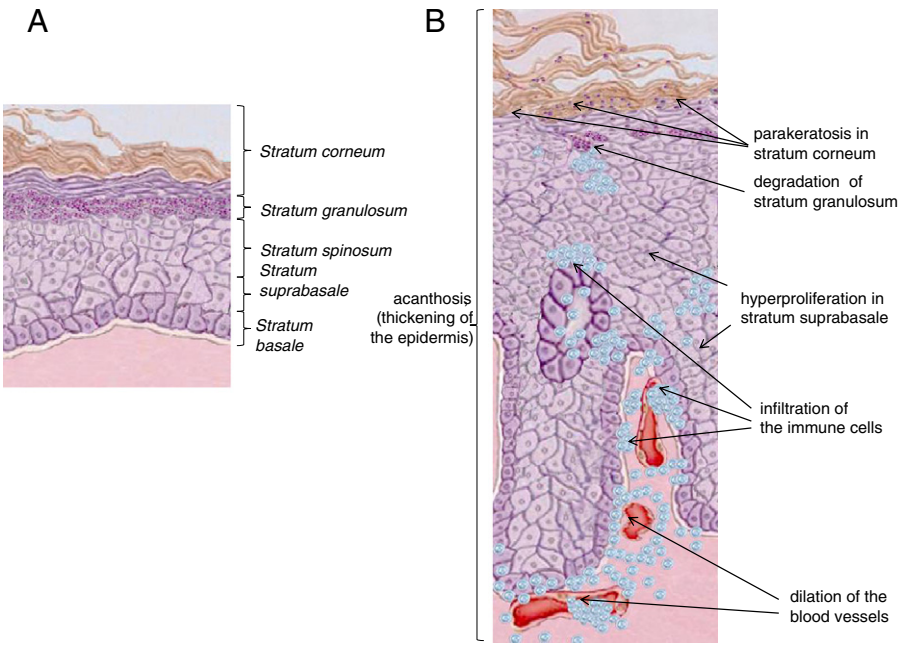

Fig. 1. Schematic representation of healthy epidermis and psoriatic plaque. A — healthy epidermis; B — psoriatic plaque.

1. Introduction

Psoriasis is a chronic skin condition driven by the activated immune system. The manifestation of psoriasis includes essential histopathological changes in the skin (Fig. 1), such as a thickening of the prickle cell layer (acanthosis) with inward growing of rete ridges (epithelial buttressing) and an enlargement of the corny layer (hyperkeratosis). The internal tissue remodeling within psoriatic plaques includes the abruption or disappearance of the granular layer (hypogranulosis), excessive cell division in the extended suprabasal layer (hyperproliferation) and parakeratosis, i.e., the presence of nucleated cells in the corny layer. The eruption of the disease leads to dilation of papillary blood vessels in the derma and an infiltration of the epidermis by immune cells, such as leukocytes, neutrophils and macrophages. These cells trigger the "cytokine storm", which is a massive secretion of proinflammatory cytokines and chemokines. In turn, the keratinocytes promote a new capillary growth *via* the production of VEGF. Moreover, psoriasis greatly accelerates cell turnover, it alters the terminal differentiation of keratinocytes, and impairs the degradation of desmosomes. This condition results in a compromising of the skin's barrier and creates opportunities for toxins and infectious agents to enter the body. This effect represents a potential health risk to the entire organism.

Matrix metalloproteinases (MMPs) are important for the stability of the extracellular matrix (ECM). They are crucial for both tissue homeostasis and the functioning of the skin in extreme and pathological conditions. Remodeling of ECM requires the cooperation between different groups of exo- and endopeptidases, because the preferential degradation of certain ECM proteins significantly changes the properties of one. In this review, we describe the role of matrix metalloproteinases in the pathogenesis of psoriasis.

2. Matrix metalloproteinases in psoriatic lesions

2.1. Collagenases

Three mammalian collagenases (MMP1, MMP8, and MMP13) cleave fibrillar collagen types I, II, III, V, and IX, which are their principle substrates, as well as several other matrix and non-matrix proteins, including growth factors (Table 1). Collagenases cleave substrates at a specific glycine–isoleucine or glycine–leucine bond. This cleavage produces triple helical fragments that are degradable to gelatin. Although several sites can exist within a given substrate, cleavage typically occurs at only one of these sites. MMP1 preferentially cleaves type III collagen and it also interacts with collagen types I and II. In contrast, type I collagen induces the expression of MMP1 (Pilcher et al., 1998). MMP1 expression is significantly elevated in psoriatic skin. However, MMP1 levels decline after a course of PUVA (Wolk et al., 2006). Our results allow us to suggest that MMP1 mRNA levels can be increased 13-fold in psoriatic skin (Starodubtseva et al., 2011). High MMP1 levels have been observed in psoriatic serum from psoriatic patients (Flisiak et al., 2006). MMP8 is primarily expressed in granulocytes, which are a part of the psoriatic infiltrate. MMP8 preferentially cleaves collagen type I over types II and III (Armstrong and Jude, 2002). Granulocytes preserve MMP8 within special granules and release it to the intercellular space upon granulocyte activation (Dorweiler et al., 2008). MMP13 is not detected in either psoriatic or healthy skin (Suomela et al., 2001).

2.2. Gelatinases

Gelatinases A and B are also referred to as 72 kDa gelatinase/type IV collagenase and 92 kDa gelatinase/type IV collagenase, respectively (Table 1). MMP2 (gelatinase A) can degrade gelatins, types I, IV, V, VII and XI collagens, fibronectin, laminin, large tenascin-C, aggrecans and elastin. MMP9 (gelatinase B) cleaves gelatins, types III, IV, V and XIV collagens, aggrecan, elastin and entactin (Birkedal-Hansen, 1995; Shipley et al., 1996a). In healthy skin, MMP2 expression can be observed in the vascular endothelium, fibroblasts and keratinocytes (Kahari and Saarialho-Kere, 1997). According to Fleischmajer et al. (2000) an elevated MMP2 expression occurs in psoriatic keratinocytes of the suprabasal layer. The authors describe two different forms of MMP2, namely, catalytically inactive pro-MMP2 and activated mature MMP2, both within and outside of psoriatic lesions (Fleischmajer et al., 2000). By comparing different types of skin, it was found that MMP2 levels increase during the transition from healthy skin to uninvolved epidermis and from uninvolved epidermis to skin lesions. Although the elevation of MMP2 expression in the psoriatic epidermis has been confirmed by another group (Simonetti et al., 2006), which reported a two-fold increase in expression, the data regarding MMP2 expression levels remain