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Presence of MUC1 in the epidermal thickening of psoriatic plaques

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Summary. Mucin 1 (MUC1) is a transmembrane glycoprotein that protects epithelial cells from injury caused by external stimuli. In addition to this role, MUC1 is involved in cell-cell adhesion, proliferation, motility, invasion and survival. In epithelial cells, MUC1 expression is regulated by binding of TNF α to TNFR1 and activation of the NFxB pathway. In human skin, MUC1 is not expressed in normal epidermis but rather in pre-malignant and malignant conditions. Nevertheless, the expression of MUC1 and its implication in psoriasis vulgaris has not been considered. Here, we show that MUC1 was present in the epidermis of psoriatic plaques observed in 11 biopsies from patients diagnosed with psoriasis vulgaris which were compared with 5 normal human skin. Interestingly, MUC1 in addition to being localized at the apical surface of some suprabasal keratinocytes, was also localized over the entire cell surface of some of these cells and some basal keratinocytes. Conversely, no MUC1 immunoreactivity was detected in the epidermis of normal skin. Additionally, we demonstrated that activated TNFR1, c-Src, IKK α/β and p50/p65 were present in the epidermal thickening. This study demonstrates the presence of MUC1 in psoriatic plaque and suggests a possible role for MUC1 during the motility, migration and survival of human keratinocytes, where activated TNFR1, c-Src and NF_zB seem to be required.

Key words: Psoriasis vulgaris, Keratinocyte, MUC1, TNFR1, NFxB

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Introduction

Psoriasis vulgaris, the most common subtype of psoriasis, is a chronic inflammatory skin disease histologically characterized by thickening of the epidermis (acanthosis) due to increased proliferation and altered differentiation of keratinocytes, parakeratosis, papillomatosis, leukocyte infiltration, granular layer reduction, dilation and tortuosity of both blood vessels and lymphatics at the papillary dermal region (Lowes et al., 2007; Cabrijan et al., 2011; Johnson-Huang et al., 2012; Perera et al., 2012). These histological alterations, proper of the psoriatic plaque, have been associated with the production of proinflammatory cytokines, including the tumor necrosis factor alpha (TNF α) and some growth factors such as epidermal growth factor (EGF), transforming growth factor alpha (TGF α), beta (TGF β) and insulin growth factor (IGF). TNFa is considered to be a key mediator in the pathogenesis of psoriasis (Lowes et al., 2007; Cabrijan et al., 2011; Johnson-Huang et al., 2012; Perera et al., 2012). In addition to the regulation of immune and inflammatory responses, it also mediates cellular responses including tissue keratinocyte remodeling, proliferation and differentiation, migration, and survival (Banno et al., 2004). These cellular responses are mediated through binding of TNF α to two cell surface receptors, TNFR1 and TNFR2, TNFR1 being the main TNF receptor expressed by keratinocytes (Banno et al., 2004). Binding

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of TNF α to TNFR1 elicits the activation of transcription factors that include the nuclear factor of transcription kappa B (NF\u03c0B) (Banno et al., 2004; Lizzul et al., 2005; Tsuruta, 2009; Perera et al., 2012). Of note, activation and translocation of NFzB mediated by the IzB Kinase (IKK) complex regulates the expression of several genes that affect epidermal keratinocyte behavior (Kaufman and Fuchs, 2000; Banno et al., 2004; Gugasyan et al., 2004; Lind et al., 2004; Lizzul et al., 2005; Abdou and Hanout, 2008; Tsuruta, 2009). Interestingly, several studies in normal and transformed epithelial cells have suggested that TNF α stimulates the expression of mucin 1 (MUC1) and that this process is mediated by NFxB/p65 (Baldus et al, 2004; Koga et al., 2007; Carson, 2008; Choi et al., 2011; Kufe, 2013). Also, MUC1 expression has been correlated with the progression of metastatic disease (Horm and Schroeder, 2013). MUC1 (also known as DF3, CA 15-3, or episialin) is a transmembrane glycoprotein that is usually localized in the apical surface of most normal secretory epithelial cells and that can be present over the entire surface of malignant epithelial cells (Wesseling et al., 1995; Rahn et al., 2001; Hollingsworth and Swanson, 2004; Kufe, 2013). MUC1, like other mucins, is considered as a molecular sensor and signal transductor that responds to external stimuli generating cellular responses which include cell proliferation, growth, differentiation, migration, invasion, survival and secretion of growth factors and cytokines (Hollingsworth and Swanson, 2004; Singh and Hollingsworth, 2006; Kufe, 2013). In human skin, MUC1 is not expressed in normal epidermis, but rather in epithelial cells in premalignant conditions that include Paget's disease, Bowen's disease, Merkel's carcinoma and Epidermolysis bullosa (Cooper et al., 2004; Chakraborty et al., 2011). Nevertheless, to our knowledge, the expression of MUC1 as well as its implication in psoriasis vulgaris has not been considered.

Taking into account the above observations, the objective of this study has been to ascertain if MUC1 is present in the epidermal thickening observed in psoriatic plaques. We also sought to determine if the expression of MUC1 could be associated to the presence and localization of TNFR1 and activated NF α B.

Materials and methods

Skin biopsies

Eleven skin biopsies from patients diagnosed with psoriasis vulgaris were retrieved from the archives of Section of Dermatopathology of SAIB. There were 7 males and 4 females, ranging in age from 23 to 43 years old, with an average of 33 years old (Table 1). Five normal human skin specimens were obtained from patients undergoing aesthetic surgery procedures. The study was performed according to the Declaration of Helsinki.

Indirect immunofluorescence

For immunofluorescence staining, deparaffinized sections were air dried and equilibrated in PBS for 10 min. Non-specific antibody staining was blocked by incubating sections in phosphate-buffered saline (PBS) containing 2% bovine serum albumin (BSA) for 1 hour at room temperature. The sections were incubated overnight at 4°C in a humid chamber with mouse monoclonal anti- human MUC1 (clone BC2) antibody (1:5 dilution) (Santa Cruz Biotechnology Inc, Santa Cruz, CA), after the sections were washed several times in PBS. Thereafter, an anti-mouse Alexa Fluor 488 secondary antibody (1:300 dilution) (Molecular Probes, Life Technologies, Oregon, OR) was applied for 30 min at RT, followed by another washing and incubation with DAPI (4',6-diamidino-2-phenylindole) at 1µg/ml (Molecular Probes, Life Technologies) in PBS for nuclear staining. Finally, the sections were again washed in PBS, and coverslipped with mounting medium (IMMU-MOUNT, Shandon, Pittsburg, PA).

For immunodetection of TNFR1 and the activated or phosphorylated forms of p50 (phospho-p50) and p65 (phospho-p65)-subunits, IKK α/β (phospho-IKK α/β) as well as of NFxB inhibitor IxBa, c-Src (phospho-c-Src) and acetylated α -tubulin some sections obtained from those samples where MUC1 was present, were incubated with a rabbit polyclonal anti human TNFR1 antibody (1:10), rabbit polyclonal anti human phospho-p50 (Ser337) antibody (1:20 dilution), rabbit polyclonal anti human phospho-p65 (Ser536) antibody (1:20 dilution), rabbit polyclonal anti human phospho-IKK α/β (Ser180/Ser181) antibody (1:50 dilution), mouse monoclonal anti- human IxBα antibody (clone H-4) (1:5 dilution), mouse monoclonal anti-human phospho-c-Src (Tyr416) (clone 9A6) antibody (1:5 dilution) (all from Santa Cruz Biotechnology) or a mouse monoclonal antihuman acetylated tubulin (clone 6-11B-1) antibody (1:70 dilution) (Sigma-Aldrich, St Louis, MO). Thereafter, an

 Table 1. Patients diagnosed with psoriasis vulgaris included in the study.

Patient	Age	Gender	Site
1	34	F	Back
2	23	F	Thigh
3	40	Μ	Forearm
4	37	М	Back
5	39	Μ	Back
6	36	Μ	Back
7	43	F	Thigh
8	30	M	Thorax
9	33	M	Back
10	28	F	Leg
11	26	M	Back

F, female; M, male

anti-rabbit Alexa Fluor 594 or anti-mouse Alexa Fluor 488 secondary antibodies (1:300 dilutions) were also applied for 30 min at RT. Negative controls were produced by the use of purified normal serum or PBS in place of primary antibody. A IX81 Olympus inverted microscope with the Fluo-View Confocal Laser



Fig. 1. Representative CLSM fluorescence images of MUC1 in psoriatic plaque and in normal skin. **a.** MUC1 is seen in some basal and suprabasal keratinocytes of the epidermal thickening. E, epidermis; D, dermis; II, inflammatory infiltrate. Blue, DAPI staining. Collagen fibers give green autofluorescence. **b.** An enlargement of figure "a" showing some basal (BC) and suprabasal cells (SBC) displaying MUC1 immunoreactivity in the apical surface and over the entire cell surface (arrows). PD, papillary dermis. Blue: DAPI staining. **c.** No MUC1 immunostaining is observed in the epidermis (E) of normal adult human skin. It appears limited to sebaceous and eccrine glands. D, dermis. **d.** Overlay of green fluorescence and Differential Interference Contrast (DIC) images. Scale bars: a, c, d, 100 μm; b, 40 μm

Scanning Microscope (CLSM) (Olympus America Inc. Melvenille, NY) was used to examine the sections. All images were acquired by using a processing software program FV10. ASW. Version 02.01.01.04 (Olympus Corporation). Image J software (NHI, Washington DC) was used for processing of contrast and brightness

Results

In vivo presence of MUC1

To ascertain whether or not MUC1 was present in the epidermal thickening observed in psoriatic plaques (11), deparaffinized sections were examined by immunofluorescence staining.

Immunofluorescence analyzed by confocal laser scanning microscopy (CLSM) revealed that some basal and suprabasal keratinocytes of the epidermal thickening displayed strong immunoreactivity for MUC1. Specifically, this transmembranal glycoprotein, in addition to being localized in a punctate and linear array at the apical surface of some basal and suprabasal keratinocytes (Fig. 1a,b), was also localized over the entire cell surface of some of the cells that were organized as a cohesive, multicellular group oriented toward papillary dermis (Fig. 1a,b). Conversely, no MUC1 immunoreactivity was detected in the epidermis of normal adult human skin, since it was limited only to the dermis, particularly to sebaceous and eccrine glands (Fig. 1c,d). No immunoreactivity was observed when the primary antibody was omitted or replaced by nonimmune serum in control sections (not shown).

In vivo TNFR1, NF κ B (p50, p65), IKK α / β and I κ B α immunolocalization

To determine if the expression of MUC1 is associated to the activation of both the TNFR1 and NF α B pathway, we examined the presence and localization of TNFR1 and the activated or phosphorylated forms of p50 (phospho-p50) and p65 (phospho-p65)-subunits, IKK α/β (phospho-IKK α/β) as well as of NF α B inhibitor I α B α in the epidermis of some psoriatic plaques where MUC1 was detected, and in the epidermis from normal patients. Both p50 and p65 were selected because they are the NF α B subunits most frequently detected in human epidermis (Kaufman and Fuchs, 2000).

Examination of the epidermis revealed a strong immunoreactivity for TNFR1 on the plasma membrane and the cytoplasm of many basal and suprabasal keratinocytes (Fig. 2a-d), while in normal epidermis this immunoreactivity appeared decreased and limited to suprabasal cells (Fig. 2e,f). Consistent with previous studies (Banno et al., 2004; Lizzul et al., 2005; Tsuruta, 2009), the presence of phospho-p50 and p65-subunits was noticeable in the cytoplasm of many basal and suprabasal keratinocytes of the epidermal thickening, as well as in the nucleus of some of these cells (Fig. 3a-d). For phospho-IKK α/β , a strong membrane and cytoplasmic immunoreactivity was observed in basal and suprabasal keratinocytes (Fig. 3e,f), whereas in the case of I \varkappa B α , moderate cytoplasmic immunoreactivity was observed in both basal and suprabasal cells (not shown). In contrast, in normal epidermis a very low membrane and cytoplasmic expression of these proteins was seen in the basal epidermis compared to suprabasal cells (Fig. 4a-f).

In vivo c-Src immunolocalization

Previous studies in transformed epithelial cells have indicated that binding TNF α to TNFR1 promotes the activation of c-Src and that activated c-Src in turn phosphorylates IKK, leading to NF α B activation and I α B α degradation (Huang et al., 2003); therefore, we sought to determine if the activated or phosphorylated c-Src (phospho-c-Src) was present in the epidermis of some psoriatic plaques where TNFR1, activated NF α B and MUC1 were evident.

Immunolocalization with anti-phosphorylated-c-Src (Tyr416) showed that this non-receptor tyrosine kinase (non-RTK) was present in the epidermal thickening. It was particularly observed in the plasma membrane and the cytoplasm of many basal and suprabasal cells (Fig. 5a,b).

In vivo acetylated a-tubulin immunolocalization

As c-Src colocalizes with microtubules (MTs) (Abu-Amer et al., 1997; Na et al., 2008; Seong et al., 2009) which are crucial for the nuclear transport of activated NF_RB and control of gene expression (Gundersen and Cook, 1999; Honore et al., 2005) and as MTs deformation is necessary for c-Src activation (Schmid-Alliana et al., 1998; Na et al., 2008), we also investigated whether the presence of activated c-Src in the epidermis of psoriatic plaques is associated with the organization and distribution of α -tubulin, one of the major components of MTs that dimerises with β -tubulin (Moss and Lane, 2006), in the epidermis of some psoriatic plaques and compared with normal epidermis. Immunolocalization with anti-acetylated α -tubulin revealed that MTs appeared spread around the cytoplasm of keratinocytes of the epidermis thickened (Fig. 6a), while in normal epidermis MTs were accumulated at the cortex of suprabasal keratinocytes (Fig. 6b).

Discussion

In the current study, we found that MUC1 is present in the epidermis of psoriatic plaques.

MUC1, in addition to being localized in the apical surface of some basal and suprabasal keratinocytes, was also found over the entire cell surface of some of those cells that were organized as a cohesive, multicellular group oriented toward papillary dermis. In contrast, no immunoreactivity was detected in the epidermis samples TNFR1



Fig. 2. Representative CLSM fluorescence images of TNFR1 in psoriatic plaque and in normal skin. **a, b.** TNFR1 is seen in many basal and suprabasal keratinocytes of the epidermal thickening. E, epidermis; D, dermis. **c, d.** An enlargement of figure "a" showing many basal (BC) and suprabasal cells (SBC) displaying a strong TNFR1 immunoreactivity in the plasma membrane and the cytoplasm. Note that this receptor is also detected in blood vessels (BV). PD, papillary dermis. **e, f.** Decreased immunostaining limited to suprabasal cells is observed in the epidermis of normal skin. E, epidermis; D, dermis. **b, d, f.** Overlay of red fluorescence and DIC images. Blue, DAPI staining. Scale bars: a, b, 70 µm; e, f, 35 µm; c, d, 100 µm.

MUC1 in psoriatic plaque Psoriatic plaque



Fig. 3. Representative CLSM fluorescence images of phospho-p50, phospho-p65, and phospho-IKK α/β in psoriatic plaque. **a-d.** Phospho-p50 and p65 are seen in the cytoplasm of many basal (BC) and suprabasal keratinocytes (SBC) of the epidermal thickening, as well as in the nucleus of some of these cells (arrows). PD, papillary dermis. **e**, **f**. Phospho-IKK α/β is seen in the membrane and cytoplasm of many basal (BC) and suprabasal cells (SBC). PD, papillary dermis. **b**, **d**, **f**. Overlay of red fluorescence and DIC images. Blue, DAPI staining. Scale bars: a-d, 50 µm; e, f, 80 µm

from healthy patients, but was indeed found in some dermal appendages. Remarkably, previous studies in human skin have revealed that MUC1 is not expressed by keratinocytes of normal epidermis but can be expressed by cells in premalignant conditions that include Bowen's disease, Paget's disease, Merkel's carcinoma and Epidermolysis bullosa (Cooper et al., 2004; Chakraborty et al., 2011). In this respect, previous



Fig. 4. Representative CLSM fluorescence images of phospho-p50, phospho-p65, and phospho-IKKα/β in normal skin. **a, c, e.** Very low membrane and cytoplasmic immunostaining of these proteins is seen in the basal cells (BC) compared to suprabasal cells (SBC). PD, papillary dermis. **b, d, f.** Overlay of red fluorescence and DIC images. Scale bar: 50µm.

in vivo and in vitro studies have demonstrated that MUC1 is usually localized in the apical surface of most normal secretory epithelial cells, whereas in epithelial carcinoma cells MUC1 is overexpressed and localized over the entire surface without obvious polarity (Wesseling et al., 1995; Rahn et al., 2001; Hollingsworth

and Swanson, 2004; Kufe, 2013). Same studies propose that MUC1 overexpression reduces cell-cell and cellextracellular matrix (ECM) adhesions, facilitating the epithelial cell motility which depends on cytoskeletal rearrangements (Wesseling et al., 1995; Rahn et al., 2001; Hollingsworth and Swanson, 2004), where non-

Phospho-c-Src



Fig. 5. a, b. CLSM fluorescence image of phospho-c-Src in psoriatic plaque. E, epidermis; D, dermis. **c, d.** At high magnification phospho-c-Src is seen in the plasma membrane and the cytoplasm of many basal (BC) and suprabasal keratinocytes (SBC) of the epidermal thickening. Note that phospho-c-Src is also detected in blood vessels (BV). PD, papillary dermis. **b, d.** Overlay of green fluorescence and DIC images. Scale bar: a, b, 100 μm; c, d, 50 μm

461

RTKs such as c-Src are involved (Hollingsworth and Swanson, 2004; Singh and Hollingsworth, 2006; Shen et al., 2008). Therefore, it is possible that the expression of MUC1 in psoriatic plaque represent a response to the elevated levels of $TNF\alpha$ that influence keratinocyte behavior by affecting cell-cell contacts and modulating cell-ECM interaction, and hence facilitating keratinocyte motility and migration. Importantly, expression of MUC1 regulated by the binding of TNF α to TNFR1 has been consistently reported in normal and transformed epithelial cells (Baldus et al, 2004; Koga et al., 2007; Carson, 2008; Choi et al., 2011; Kufe, 2013). Moreover, induction of cytoskeletal reorganization and stimulation of keratinocyte migration by TNFα through NF_αB during cutaneous inflammatory disease has also been proposed (Banno et al., 2004). Consequently, we also investigated the presence of TNFR1 and activated or phosphorylated forms of p50 and p65-subunits, IKK α/β and $I \varkappa B \alpha$ in the epidermis of some psoriatic plaques where MUC1 was detected, as well as in the epidermis samples from healthy patients. Immunofluorescence revealed a strong immunoreactivity from TNFR1 on the plasma membrane and the cytoplasm of many basal and suprabasal keratinocytes in the epidermal thickening, while in normal epidermis this expression was decreased and limited to suprabasal cells. Evidence of augmented levels of TNF α and TNFR1 expression associated with cell proliferation or cell survival and differentiation has been reported by others after injury and during cutaneous inflammation (Banno et al., 2004). Also, studies in animal models have indicated that TNFR1 is required for skin inflammation and epidermal hyperplasia (Lind et al., 2004).

Concerning the activated forms of p50 and p65subunits, IKK α/β and I \varkappa B α , immunofluorescence also evidenced a strong immunoreactivity for these proteins in the epidermis of some psoriatic plaques where MUC1 was found, supporting their important role in the pathogenesis of psoriasis. These findings are interesting if we consider that in psoriatic epidermis $TNF\alpha$ production by inflammatory cells and keratinocytes provokes activation of NFxB (Banno et al., 2004; Lizzul et al., 2005; Tsuruta, 2009), and that in normal and transformed epithelial cells TNFa, through the activation of NF₂B, stimulates the expression of MUC1 (Baldus et al, 2004; Koga et al., 2007; Carson, 2008; Choi et al., 2011; Kufe, 2013). Thus, it is possible to hypothesize that binding of TNF α to TNFR1 could promote NFxB activation which would be accompanied by the modulation of specific genes to control not only proliferation and survival of keratinocytes in psoriatic epidermis, but also the expression of MUC1. Importantly, it has been proposed that a link between the activated TNF α , NF κ B and the expression of MUC1

acetylated tubulin



Normal skin



Fig. 6. Overlay of green fluorescence and DIC images of a psoriatic plaque and a normal skin immunostained with an antibody to acetylated α-tubulin. **a.** Microtubules appear spread and around the cytoplasm of basal (BC) and suprabasal keratinocytes (SBC) of the epidermis thickened. **b.** Microtubules are accumulated at the cortex of basal (BC) and suprabasal keratinocytes (SBC) of normal epidermis. PD, papillary dermis. Scale bar: 50 μm.

occurs during the progression of certain carcinomas (Carson, 2008; Kufe, 2013). Thus, our observations as well as those from other studies are compatible with the hypothesis that the psoriatic plaque could convert to cancer (Nickoloff et al., 2005; Pouplard et al., 2013). However, this association is still a matter of debate (Pouplard et al., 2013).

In this study, we also found that the activated c-Src was present in the plasma membrane and cytoplasm of many basal and suprabasal keratinocytes of the epidermal thickening. We believe that this localization of c-Src may be associated with the binding of TNFR1 and the activation of NF \varkappa B mediated by IKK α/β . Consistent with this, studies in transformed epithelial cells have provided evidence that binding of TNFR1 to TNFR1 promotes activation of c-Src, which then phosphorylates IKK, leading to the activation of NF \varkappa B and I \varkappa B α degradation (Huang et al., 2003).

We also found alterations in tubulin organization and distribution in the keratinocytes of some psoriatic plaques where activated c-Src, phospho-IKK α/β and MUC1 were present. We suggest that the activation of c-Src would be associated with these alterations considering that MTs deformation is necessary for c-Src activation (Schmid-Alliana et al., 1998; Na et al., 2008) and that TNF α causes MTs disassembly in endothelial cells (Petrache et al., 2003).

Consistent with our findings and studies mentioned here, we hypothesize that in keratinocytes of psoriatic plaque, binding of TNF α to TNFR1 may cause alterations in the organization of the cytoskeleton, particularly the MTs, which induce the activation of c-Src. Activated c-Src phosphorylates IKK complex leading to the activation and nuclear translocation of NF κ B. At the nucleus, NF κ B may cause the expression of MUC1. Once installed in the plasma membrane, MUC1 may aid keratinocyte motility and migration.

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