Beta-catenin expression in psoriasis

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ABSTRACT

Background: Psoriasis is a common inflammatory skin disease characterized by abnormal keratinocyte proliferation and differentiation. Beta-catenin participates in intercellular adhesion. Catenins are proteins found in complexes with cadherin cell adhesion molecules of cells. The role of catenin in regulating keratinocyte stem cell differentiation and hair follicle morphogenesis has been extensively reported. **Aims and Objectives:** is to study β-catenin expression in lesional and non-lesional psoriatic skin to throw light upon its possible role in the pathogenesis of psoriasis. **Materials and Methods:** Biopsies were taken from 20 patients with psoriasis vulgaris and from 10 normal controls. The distribution of Beta catenin was investigated using polycolonal rabbits B-catenin antibody-1 by immunohistochemical method. **Results:** In this study membranous β-catenin expression was significantly demonstrated in the control group then the non-lesional areas in comparison to the lesional areas ($P < 0.001$). Nuclear β-catenin staining expression was significantly more demonstrated in lesional and non-lesional areas in comparison to the control cases ($P < 0.001$). **Conclusions:** The down regulation of membranous β-catenin expression in lesional psoriatic skin might reflect a useful phenotypic marker of hyperprolifration of keratinocytes in psoriasis. Moreover, the mild down regulation of membranous β-catenin expression in non lesional psoriatic skin may provide clues about incipient structural abnormalities in the pathogenesis of psoriasis, providing an early diagnostic indicator for evolution to a generalized form of the disease. Nuclear β-catenin expression was not found in the control group but was demonstrated in lesional and moderately in non-lesional reflecting its role in kerationcyte proliferation.

Key words: Beta-catenin, psoriasis, pathogenesis-immunohistochemical

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INTRODUCTION

Psoriasis is a common inflammatory skin disease characterized by abnormal keratinocyte proliferation and differentiation, angiogenesis, immune activation, and inflammation.[1,2] Although there is evidence for immune activation with lymphocyte infiltration in the psoriatic epidermis, there also exists evidence of primary keratinocyte defects.[3] In the psoriatic epidermis, proteins that are expressed in the early stage of keratinocyte differentiation such as keratinocyte transglutaminase are expressed earlier and in a greater amount.[4] In contrast, the expression of proteins that are usually expressed in the later stages of kertinocyte differentiation such as filaggrin are downregulated in the epidermis of psoriatic plaques.[5] There is accumulating evidence that proteins that mediate intracellular adhesions are involved in keratinocyte differentiation.[6] One candidate for this is beta-catenin (β-catenin) a 94-kDa protein that participates in intercellular adhesion, β-catenin links E-cadherin to the actin cytoskeleton through alpha-catenin.[7] Catenins are proteins found in complexes with cadherin cell adhesion molecules of cells. The first two catenins that were identified became known as α-catenin and β-catenin. Alpha-catenin can bind to β-catenin and can also bind actin. β-catenin binds the cytoplasmic domain of some cadherins.[8] Overexpression of the basal layer cadherins in suprabasal epidermis leads to increased cytoplasmic activity of β-catenin and increased β-catenin transcriptional activation. This overexpression of the basal layer cadherins results in abnormal keratinocyte differentiation. The role of β-catenin in regulating keratinocyte stem cell differentiation and hair follicle morphogenesis has been extensively reported. Doglioni *et al*.[9] studied β-catenin in human skin tumors and noted that β-catenin was occasionally present in both nuclear and cytoplasmic locations in the basal cells, scattered differentiated keratinocytes and luminal cells of the sebaceous glands. To gain an insight

into the role of β-catenin on the regulation of keratinocytes and further investigate the pathogenesis of psoriasis, we compared the expression of β-catenin in normal human and psoriatic skin.

MATERIALS AND METHODS

This study was carried out in 20 psoriasis vulgaris patients with 10 non-psoriatic subjects as controls. These patients were selected randomly from the dermatology outpatient clinic, Faculty of Medicine, Menoufia University and Sheibin El-Kom Educational Hospital during the period from April 2009 to June 2010. All patients instructed to stop all forms of medication one month prior to optaining a skin biopsy. Patients were subjected to the following: History taking and clinical examination. Two skin biopsies were taken - one from the representative psoriatic lesion and the other from nonlesional skin under local xylocaine anesthesia. The diagnosis of psoriasis was based on both clinical and histopathological examination by hematoxylin and eosin stain. Informed consent was obtained from all patients. This study was approved by the Ethics Committee of Menoufia University.

Immunohistopathological

The improved biotin-streptavidin amplified detection system was used in the work. The primary antibody was rabbit polyclonal antibody (0.1 ml) (Lab-vision, Westinghouse, USA).

Interpretation of beta-catenin expression

Beta-catenin expression was assessed according to:

- Intensity: Weak (+) moderate (++) or strong expression (+++)
- Cell counting: The number of β-catenin positive nuclei and total nuclei in the upper half of the suprabasal region were counted in four individual fields from each biopsy specimen. Then the percent positivity was calculated. For further statistical analysis, cases were divided into two groups: Suprabasal nuclear β-catenin staining <50%, and >50%
- Location: Membranous or nuclear location of expression.

Statistical analysis

Data was collected and statistically analyzed using Statistical Package (IBM Corporation) for Social Sciences version 9 program and StatView software (IBM Corporation). The following statistical measures were employed:

- Arithmetic mean (X) for central tendency
- Percentage (%). B-Analytic statistics:
  - Student's *t*-test to compare two quantitative variables
  - Chi-square test (χ^2) to compare between qualitative variables $P < 0.05$ was considered as statistically significant (S).

RESULTS

The age of the patients ranged from 12 to 75 years with a mean age 49.7 ± 15.2 years. Among 20 patients suffering from psoriasis, 8 were males and 12 were females. The duration of the disease varied from 6 months to 19 years with a mean of 5.67 ± 0.5 years. In all clinically diagnosed patients, histopathology revealed parakeratosis, absent granular cell layer, Munro microabscesses, acanthosis, spongiosis, and papillomatosis in the epidermis. Dermal capillary dilatation and inflammatory cells were present in all cases and edema in some cases [Figure 1a and b].

Immunohistochemical results of beta-catenin staining expression

In the present study, we made a comparative study of the structural organization of the epidermis and in particular the intercellular junctions between lesional and nonlesional skin of psoriasis patients. The presence and distribution of β-catenin was analyzed by immunohistochemistry of normal skin, and lesional and nonlesional psoriatic skin. In the normal epidermis β-catenin

Table 1: Comparison between membranous beta-catenin staining expression in control, and lesional and nonlesional skin of psoriasis

Membranous staining	No. (%)			χ^2	*P* value
	Mild (+)	Moderate (++)	Strong (+++)		
Control	0 (0.0)	0 (0)	10 (100.0)	34.9	<0.001*
Lesional skin	7 (35.0)	13 (65.0)	-		
Nonlesional skin	-	7 (35.0)	13 (65.0)		

*Highly significant (*P*<0.001). Membranous beta-catenin expression was significantly demonstrated in the control group, followed by nonlesional areas and least in lesional areas of psoriasis (*P*<0.001)

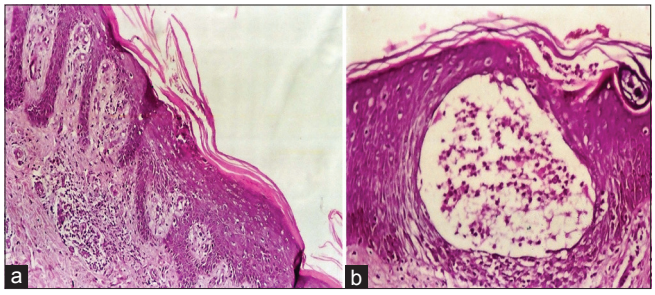

Figure 1: (a) Psoriasis lesion with Munro microabscess in psoriasis (H and E, ×200). (b) Psoriasis lesion with epidermal, parakeratosis, acanthosis, spongiosis, absent granular cell layer and dermal capillary dilatation and inflammatory cells (H and E, ×400)

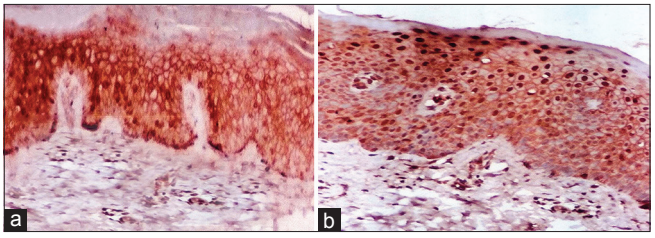

Figure 2: (a) Skin of a normal control showing membranous beta-catenin (β-catenin) staining expression and few suprabasal nuclear stains (IPS, ×200). (b) Few strong nuclear suprabasal β-catenin staining expression in nonlesional skin of psoriasis (Immunoperioxedase stain, ×200)

was detected solely on the cell membrane of the basal cells and lower spinous cells [Table 1, Figure 2a]. This protein showed a continuous well defined distribution at the borders of these cells. In nonlesional psoriatic skin, there were a few suprabasal cells showing strong nuclear β-catenin expression [Table 2, Figure 2b]. In lesional psoriatic skin, there was a positive nuclear suprabasal β-catenin expression and negative β-catenin expression in parakeratotic cells [Table 2, Figure 3a]. There was a strong nuclear with membranous β-catenin expression in psoriatic skin [Figure 3b]. At the junction between nonlesional and lesional skin there was membranous β-catenin expression in nonlesional skin and both membranous and nuclear β-catenin expression in lesional psoriatic skin [Figure 4a]. In nonlesional psoriatic skin, there was a membranous β-catenin expression along with a positive dermal inflammatory component [Figure 4b]. There was positive nuclear and cytoplasmic β-catenin expression in normal hair follicles [Figure 4c].

DISCUSSION

Catenins are cytoplasmic proteins alpha, beta, gamma, and p120 proteins. They play an important role in the maintenance of normal tissue architecture.[10] Catenins are cell-cell adhesion molecules that also maintain intracellular adhesiveness through cytoplasmic catenin proteins that bind the microfilaments to the cytoskeleton.[11] β-catenin is not required for keratincoyte proliferation, but has been shown to regulate keratinocyte stem cells and hair follicle morophogenesis.[12] With regard to membranous β-catenin staining expression, it was significantly demonstrated in the control group and nonlesional areas in psoriatics as compared to lesional areas in psoriatics. This reflects its role of β-catenin as an adhesion molecule in uninvolved and normal skin. Nuclear β-catenin staining expression was significantly demonstrated in lesional and nonlesional skin of psoriatics as compared to controls. This finding agreed with previous work done by Stojadinovic *et al*.,[13] who studied the role of β-catenin in the inhibition of epithelization and wound healing. They did not find any nuclear β-catenin in normal epidermis. Furthermore in the study done by Butz and Larue,[14] it was found that β-catenin was detected only on the cell membrane of the normal epidermis and normal hair follicles with no nuclear β-catenin staining detected. Our findings are in agreement with those of Hampton *et al*.,[15] who found increased nuclear β-catenin in suprabasal lesional psoriatic epidermis. Some nuclear β-catenin was also detected in nonlesional psoriatic skin, but much less than in lesional psoriatic skin. The distribution of β-catenin in the membrane of normal cells more than in the nuclear location

Table 2: Comparison between suprabasal nuclear beta-catenin staining expression in controls, and lesional and nonlesional skin of psoriasis

Group/subset	Nuclear beta-catenin staining expression (No. (%))			χ^2	*P* value
	0	<50	>50		
Control	10 (100)	-	-	64.9	<0.001*
Lesional skin	-	9 (45.0)	11 (55.0)		
Nonlesional skin	-	19 (96.0)	1 (5.0)		

*Highly significant (*P*<0.001). Nuclear beta-catenin staining expression was significantly more expressed in lesional and nonlesional areas of psoriasis in comparison to controls (*P*<0.001)

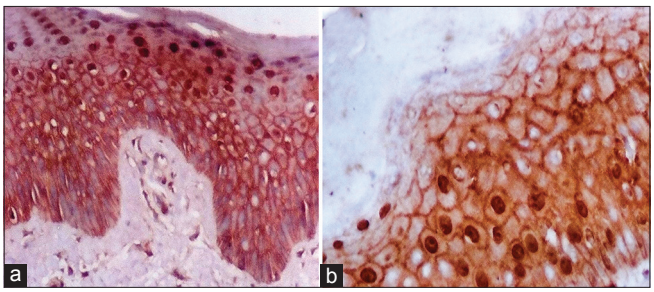

Figure 3: (a) Nuclear suprabasal beta-catenin (β-catenin) staining expression in all layers of epidermis except the parakeratotic and cornified layers of a psoriasis lesion (Immunoperioxedase stain, ×400). (b) Strong nuclear with membranous β-catenin expression and negative expression in the parakeratotic layer of a psoriasis lesion (Immunoperioxedase stain, ×400)

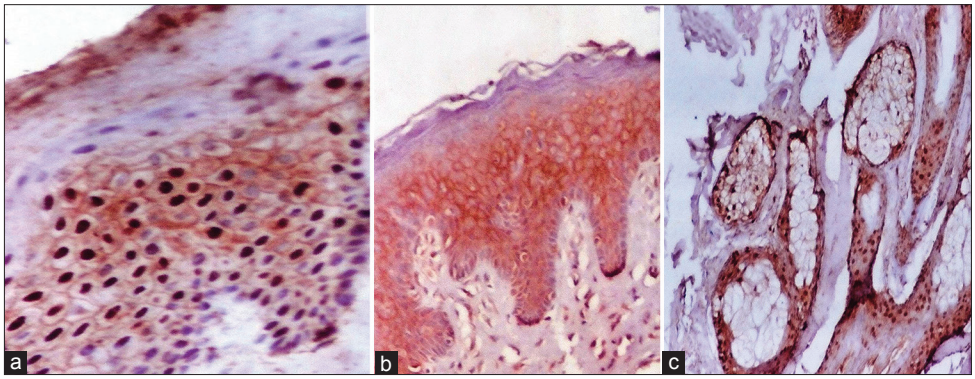

Figure 4: (a) Junction between nonlesional (right) and lesional (left) skin of psoriasis showing only membranous staining (nonlesional) while both membranous and nuclear beta-catenin (β-catenin) expression is seen in lesional skin (IPS, ×400). (b) Membranous β-catenin expression together with positive dermal inflammatory components in nonlesional skin of psoriasis (Immunoperioxedase stain, ×200). (c) Nuclear and cytoplasmic β-catenin expression in normal hair follicle matrix cell (Immunoperioxedase stain, ×400)

may be due to its role in the establishment and regulation of adherens junctions by interaction with E-cadherin through alpha catenin with the actin cytoskeleton.[15] Furthermore, some studies suggest that β-catenin may be translocated from the nucleus back to the cell membrane, presumably through a soluble, cytosolic intermediate state.[16] Watt and Collins,[17] found the same result in their study of the role of nuclear β-catenin in colorectal tumors. Watabe and Miyazono,[17] studied nuclear localization of β-catenin in the hair matrix cells and differentiated keratinocytes. They found less nuclear β-catenin than membranous β-catenin in normal skin cells. Zhou *et al*.,[18] showed a significant increase in nuclear β-catenin within the suprabasal layers in the involved psoriatic epidermis. Also, Zhou *et al*.,[18] observed a marked decrease in membranous β-catenin at the same level as increased in the nuclear β-catenin. They suggested that in involved suprabasal psoriatic epidermis, an excess amount of free unphosphrylated β-catenin enters the cytoplasm and subsequently translocates to the nucleus. Zhou *et al*.,[18] showed in their study that there was no significant increase in the expression of β-catenin in both membranous and nuclear locations in nonlesional suprabasal cells of psoriatics. Normal skin and the uninvolved psoriatic epidermis might transcriptionally active β-catenin released into the cytoplasm that would likely be rapidly targeted for ubiquitination to prevent abnormal signaling events. This leads to little nuclear β-catenin in uninvolved or normal suprabasal epidermis.[18] In a study done by Li *et al*.,[19] who studied the expression of E-cadherin and β-catenin in the lesional skin of patients with active psoriasis, there was downregulation of β-catenin expression, which was found in the granular layer and basal layer of the psoriatic lesions only.

CONCLUSION

In normal control group β-catenin was mainly demonstrated as membranous pattern of expression; this reflects its role as an adhesion molecule. The downregulation of membranous β-catenin expression in lesional psoriatic skin suggests that it could be a useful phenotypic marker for the hyperprolifration of keratinocytes in psoriasis. Moreover, the mild downregulation of membranous β-catenin expression in nonlesional psoriatic skin may provide clues about impending structural abnormalities in the pathogenesis of psoriasis, providing an early diagnostic indication for evolution to a generalized form of the disease. Nuclear β-catenin expression was not found in the control group but demonstrated in lesional and moderately in nonlesional skin of psoriatics reflecting its role in kerationcyte proliferation. The nuclear and cytoplasmic expression of β-catenin in normal hair follicle provides evidence suggesting that it plays an important role in keratinocyte differentiation.

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