

IMMUNOHISTOCHEMICAL EXPRESSION OF E-CADHERIN AND BETA-CATENIN IN PSORIASIS

Thesis

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Abstract:

Background: Psoriasis is a common inflammatory skin disease characterized by abnormal keratinocyte proliferation and differentiation, both E-cadherin and β -catenin are important for epidermal intercellular adherence in addition β -catenin also acts as a transcription factor as part of the Wnt signalling pathway.

Objectives: To assess the presence and distribution of E-cadherin and β -catenin in psoriasis in order to investigate their possible role in the pathogenesis of psoriasis.

Patients and Methods: Thirty patients having psoriasis vulgaris were recruited from the outpatient clinic, dermatology department. Faculty of Medicine, Cairo University as well as twenty (age and sex matched) volunteers (psoriasis free) with healthy skin appearance (as a control group). All patients were subjected to complete history taking with special emphasis on the duration of the disease, dermatological examination and registration of PASI score. Both patients and controls underwent skin biopsy. H& E staining was performed for histopathological examination and a grading system with a numerical value assigned for each biopsy was taken from all cases. Immunohistochemical staining was performed to detect both membranous E-cadherin and β -catenin expression and distribution in both cases and control groups.

Results: There was a highly significant difference between cases and control group regarding to immunostaining of both E-cadherin and β -catenin in each of (granular, upper spinous, and basal skin layers) with high mean among control, and no significant difference in immunostaining between study groups regarding (lower spinous layer). There was a highly significant negative correlation between the used histologic grading score and immunohistochemical staining of both E-cadherin and β -catenin in all skin layers. There was no significant correlation between the duration of disease and the immunohistochemical staining of both E-cadherin and β -catenin in different skin layers. Similarly the PASI score did not correlate with the immunohistochemical staining of both E-cadherin and β -catenin and the used histologic grading score.

Conclusion: In psoriasis there are alterations in the organization of adherence junction proteins especially E-cadherin and β -catenin, and these alterations could contribute to modify interactions between neighboring cells, leading to inadequate function of the epithelial skin layers, and also enhance the proliferative activity in the affected epidermis.

Key words: psoriasis vulgaris, E-cadherin, β -catenin

Contents

		<i>Page</i>
▶	Introduction and aim of the work	
▶	Review of the Literature	
	<i>Psoriasis Vulgaris: pathology and pathogenesis</i>	
	<i>E-cadherin and Beta-catenin</i>	
	<i>E-cadherin and Beta-catenin in psoriasis</i>	
▶	Patients and Methods	
▶	Results	
▶	Discussion	
▶	Summary, Conclusion and Recommendations	
▶	References	
▶	Arabic summary	

List of Tables

		<i>Page</i>
<i>Table (A)</i>	Elements of the Psoriasis Area and Severity Index (PASI)	
<i>Table (B)</i>	Histologic grading system check list	
<i>Table (1)</i>	Comparison between case and control groups regarding to immunohistochemical staining	
<i>Table (2)</i>	Distribution of the cases according to their histological grading and the average of their immunohistochemical staining	
<i>Table (3)</i>	Correlation between different layers immunohistochemical staining and histologic grading score among cases	
<i>Table (4)</i>	Correlation between different layers immunohistochemical staining and PASI score among cases	
<i>Table (5)</i>	Correlation between different layers immunohistochemical staining and the disease duration among cases	

List of Abbreviations

AJ	Adherens Junction
APCs	Antigen Presenting Cells
DCs	Dendritic cells
E/β protein complex	E-cadherin/ β -catenin protein complex
EGF	Endothelial Growth Factor
GSK-3β	Glycogen Synthase Kinase-3 β
GSKBP	Glycogen Synthase Kinase-3 β Binding Protein
HSPs	Heat Shock Proteins
ICAM	Intercellular adhesion molecule
IFN-γ	Interferon- γ
IL	Interleukin
iNOS	Inducible Nitric Oxide Synthase
LEF	Lymphocyte Enhancer Factor
LFA	Lymphocyte Functional Antigen
MHC	Major Histocompatibility
NF	Nuclear Factor
PASI	Psoriatic Area and Severity Index
TCF	T-cell Factor
TGF	Transforming Growth Factor
Th	T helper
TLRs	Toll Like Receptors
TNF-α	Tumor Necrosis Factor- α
Treg	T regulatory
VEGF	Vascular Endothelial Growth Factor
VPF	Vascular permeability Factor

List of Figures

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Introduction & Aim of the work

Psoriasis is a common inflammatory skin disease characterized by abnormal keratinocyte proliferation and differentiation, angiogenesis, immune activation and inflammation (**Ghorpade, 2004**).

Although there is evidence for immune activation with lymphocyte infiltration in psoriatic epidermis, there is also evidence for primary keratinocyte defects (**Lebwohl, 2003**).

In active psoriasis; keratinocyte proliferation outside the basal layer suggests an alteration in cell–cell interactions. The molecular alterations in epidermal barrier function and the mechanisms underlying the perturbed state of proliferation and differentiation in psoriatic epidermis remain poorly understood (**Griffith et al., 2007**).

Keratinocytes interact with each other through intercellular junctions to regulate cellular shape, proliferation, and the passage of ions and molecules through the paracellular pathway (**Brander et al., 2002**).

E-cadherin is important for epidermal intercellular adherence because it is required for the adhesive properties of keratinocytes and skin differentiation (**Perl et al., 1998**). Loss of E-cadherin could therefore lead to progressive hyperproliferation in epidermis (**Christopher et al., 2004**).

β -catenin, a 94-kD is a protein which participates in intercellular adhesion as part of the adherens junctions, as it links E-cadherin to the actin cytoskeleton via α -catenin, so E-cadherin and β -catenin, are thus referred to as E/ β protein complex (**Nelson and Nusse, 2004**).

β -catenin has a dual function as a component of intercellular adherens junctions and also as a transcription factor as part of the Wnt signalling pathway (**Miravet et al., 2003**). There is accumulating evidence that β -catenin is also involved in cellular differentiation (**Reya and Clevers, 2005**).

In normal skin tissues, E-cadherin and β -catenin are found uniformly distributed within all layers of normal epidermis particularly at the sites of cell-cell junctions (**Hampton et al., 2007**).

Alicia et al. (2006) found that the pattern of the E/ β protein complex staining in the skin of psoriatic patients differed from that seen in normal skin; suggesting that in these cases alterations in the organization of adherens junction (AJ) proteins could contribute to modify interactions between neighboring cells, leading to inadequate function of the epithelial layers.

To the best of our knowledge, studies that have investigated the role of E-cadherin and β -catenin in psoriasis are still few in number and more studies are necessary to understand fully the situation.

So we aimed by this work to assess the presence and distribution of membranous E-cadherin and β -catenin in psoriasis in order to investigate their possible role in the pathogenesis of psoriasis.

Psoriasis Vulgaris: Pathology and Pathogenesis

Psoriasis is an ancient disease, Hippocrates (460–377 BCE) used the term psora, meaning “to itch” (**Nickoloff and Nestle, 2004**). It is a common, genetically determined, inflammatory and proliferative disease of the skin, the most characteristic lesions consisting of chronic, sharply demarcated, dull-red, scaly plaques, particularly on the extensor prominences and in the scalp (**Krueger and Ellis, 2005**).

It affects about 2% of the world’s general population, and its incidence differs according to race, sex and age (**Christophers, 2001**).

The disease is enormously variable in duration and extent and morphological variants are common (**Krueger and Ellis, 2005**). It can begin at any age, although epidemiological studies demonstrate that it most commonly appears for the first time between the ages of 15 and 25 years, with a second peak occurring at 55–60 years (**Ferrandiz et al., 2002**).

Many morphological variants of psoriasis are present, among which psoriasis vulgaris is the commonest affecting 80 to 90% of people with psoriasis (**Pandey, 2010**).

Clinically: Psoriasis vulgaris is characterized by pink to red papules and plaques (Figure A). The lesions are of variable size, sharply demarcated, dry, and usually covered with layers of fine, silvery scales. As the scales are removed by gentle scraping, fine bleeding points usually are seen, the so-called Auspitz sign (**Freiman et al., 2006**).

The scalp, sacral region, and extensor surfaces of the extremities are commonly involved. Involvement of the nails is common; the most frequent alteration of the nail plate surface is the presence of pits (**Stern et al., 2004**).

Pustules generally are absent in psoriasis vulgaris, although pustules on palms and soles occasionally occur. Rarely, one or a few areas show pustules, and this is referred to as “psoriasis with pustules” (**Augey et al., 2006**).

Oral lesions such as stomatitis areata migrans (geographic stomatitis) and benign migratory glossitis may be seen in psoriasis vulgaris as well as in generalized pustular psoriasis (**Femiano, 2001**).

Psoriatic arthritis characteristically involves the terminal interphalangeal joints, but frequently the large joints are also affected so that a clinical differentiation from rheumatoid arthritis often is impossible. However, the rheumatoid factor is generally absent (**Gladman, 2004**).

Traditionally, the severity of psoriasis is measured using various symptom scores as body surface area involved, psoriatic area and severity index (PASI), self-administrated PASI, National Psoriasis Foundation Score, Dermatology Life Quality Index, Salford Psoriasis Index, and the Lattice System Physician Global Assessment. However the most often used psoriasis score is (PASI) (**Finlay, 2005**).

The Histopathologic Picture of Psoriasis vulgaris (Figure A): The picture of psoriasis varies considerably with the stage of the lesion and usually is diagnostic only in scaling papules and near the margin of advancing plaques (**Blauvelt et al., 2003**).

The earliest pinhead-sized macules or smooth-surfaced papules show a subtle histologic picture with a preponderance of dermal changes. At first, there is capillary dilatation and edema in the papillary dermis, with a lymphocytic infiltrate surrounding the capillaries. The lymphocytes extend into the lower portion of the epidermis, where slight spongiosis develops. Then focal changes occur in the upper portion of the epidermis, where granular cells become vacuolated and disappear, and mounds of parakeratosis are formed (**Mobini et al., 2005**).

The neutrophils usually are seen only at the summits of some of the mounds of parakeratosis and appear scattered through an otherwise orthokeratotic cornified layer. These mounds of parakeratosis with neutrophils represent the earliest manifestation of Munro microabscesses. At this stage, which is characterized clinically by an early, scaling papule, a histologic diagnosis of psoriasis can often be made (**Halevy et al., 2006**).

In some cases, when there is marked exocytosis of neutrophils, they may aggregate in the uppermost portion of the spinous layer to form small spongiform pustules of Kogoj. Lymphocytes remain confined to the lower epidermis, which, as more and more mitoses occur, becomes increasingly hyperplastic. The epidermal changes at first are focal but later on become confluent, leading clinically to plaques (**Van de Kerkhof and Lammers, 1987**).

In the fully developed lesions of psoriasis, the histologic picture is characterized by acanthosis with regular elongation of the rete ridges with thickening in their lower portion, thinning of the suprapapillary epidermis with the occasional presence of small spongiform pustules, pallor of the upper layers of the epidermis, diminished to absent granular layer, confluent parakeratosis, the presence of Munro microabscesses;

elongation and edema of the dermal papillae, and dilated and tortuous capillaries (**Mobini et al., 2005**).

Of all the listed features, only the spongiform pustules of Kogoj and Munro microabscesses are truly diagnostic of psoriasis, and, in their absence, the diagnosis rarely can be made with certainty on a histologic basis (**Trozak, 1994**).

The rete ridges show considerable elongation and extend downward to a uniform level, resulting in regular acanthosis. They are often slender in their upper portion but show thickening (“clubbing”) in their lower portion. Not infrequently, neighboring rete ridges are seen to coalesce at their bases (**Weedon and Strutton, 2002**).

Usually, intercellular and intracellular edema are absent in the rete ridges and keratinocytes located well above the basal layer show deep basophilia. In addition, mitoses are not limited to the basal layer as in normal skin, but are also seen above the basal layer. This, together with a considerable lengthening of the basal cell layer due to elongation of the rete ridges, results in a great increase in the number of mitoses. This increase has been calculated to be 27 times the number of mitoses in uninvolved skin (**Marshall, 1991**).

The suprapapillary epidermis appears relatively thin in comparison with the markedly elongated rete ridges, and the cells in the upper layers of the epidermis may appear enlarged and pale-stained as a result of intracellular edema (**Mark et al., 1989**).

The epidermal cells located immediately beneath the parakeratotic cornified layer may be intermingled with neutrophils. The histologic picture is then that of a small spongiform pustule of Kogoj. Although it is only a micropustule, it is nevertheless of the same type as the much larger macropustules seen in pustular psoriasis. Such a spongiform pustule,