Evaluation of the effect of NB-UVB phototherapy on HMGB1 expression in chronic plaque type psoriasis

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List of Abbreviations

AMPs: Antimicrobial peptides

APCs: Antigen-presenting cells

cAMP: Cyclic adnosine monophosphate

CLA: Cutaneous lymphocyte antigen

DC: Dendritic cells

DDC: Dermal dendritic cells

DNA: Deoxyribonucleic acid

ECAM: Endothelial cell adhesion molecule.

EGF-R: Epidermal growth factor receptor

ELISA: Enzyme linked immunosorbent assay

GM-CSF: Granulocyte-macrophage colony-stimulating factor

H: Histone

HLA: Human leucocyte antigen

HPV: Human papilloma virus

HMGB1: High mobility group box 1

ICAM: Intracellular adhesion molecule

IFN-α: Interferon alpha

IFN-γ: Interferon gamma

IGF-1: Insulin-like growth factor-1

IκB: Inhibitors of kappa-B

IL: Interleukin

Kc: Keratinocyte

KGF: Keratinocyte growth factor

LFA: Lymphocyte functional antigen

MTX: Methotrexate

MHC: Major histocompatibility complex

mRNA: Messenger ribonucleic acid

mTOR : Mammalian target of rapamycin

N: Number

NAD: Nicotinamide adenine dinucleotide

NAM: Nicotinamide

NF-IL-6: Nuclear factor IL-6

NF-κB: Nuclear factor kappa-B

NGF: Nerve growth factor

NK: Natural Killer

PASI: Psoriasis area and severity index

PBMCs: Peripheral blood mononuclear cells

PGE2: Prostaglandin E2

PV: Psoriasis vulgaris

RNA: Ribonucleic acid

rRNA: Ribosomal ribonucleic acid

SD: Standard deviation

SLE: Systemic lupus erythematosus

TCR: T cell receptor

TGF: Transforming growth factor

Th: T helper

TLRs: Toll like receptors

TNF-α: Tumor Necrosis Factor-alpha

UV: Ultraviolet

VCAM: Vascular cell adhesion molecule

VEGF: Vascular endothelial growth factor

VIP: Vasoactive intestinal peptide

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Introduction

Psoriasis vulgaris is a common, chronic relapsing, remitting immune mediated skin disease characterized by red, scaly patches, papules and plaques, which is usually itchy ***(Menter et al., 2008).*** The disease affects 2-4% of the general population ***(Parisi et al., 2013).***

There are five main types of psoriasis: plaque, guttate, inverse, pustular, and erythrodermic ***(University of California et al., 2013).*** Plaque psoriasis is the most common form and typically manifests as red and white scaly patches on the top layer of the skin. Plaques frequently occur on the skin of the elbows and knees, but can affect any area including the scalp, palms of hands and soles of feet, and genitals.

Fingernails and toe-nails are frequently affected and can be seen as isolated sign. Inflammation of the joint in the context of psoriatic disease, known as psoriatic arthritis affect up to 30% of the individual with psoriasis ***(Jain et al., 2012).***

The causes of psoriasis are not fully understood. Psoriasis is not purely skin disorder. Psoriasis is a genetic disease of dysregulated inflammation. The mechanism of inheritance is not completely defined. Psoriasis is an immune-mediated skin and-or joint inflammatory disease in which intralesional inflammation primes basal stem keratinocytes to hyperproliferate. Resolution of psoriasis is associated with decreased lesional infiltration of T cells, dermal dendritic cells, Langerhans cells, and neutrophils, and decreased expression of TNF, interferon and IL12-23 dependent genes. Environmental factors also play a role in the pathogenesis of psoriasis including drugs, skin trauma, infection and stress ***(Habif et al,. 2010).***

High Mobility Group box1 (HMGB1) is a conversed protein located in all mammalian nuclei at high concentrations. It acts as a pro-inflammatory cytokine in both acute and chronic inflammatory condition such as septic shock, acute lung injury ***(Dumitriu et al., 2006).*** It is actively released from lipopolysaccharide, tumor necrosis factor α and interleukin1 (IL-1), activated monocytes, macrophages and other cell types.

It can also be passively released from dying damaged cells during necrosis and during the late phase of apoptosis. Extracellular HMGB1 exerts its biological actions by binding to cell surface receptors such as receptors of advanced glycation end product, toll-like receptors (TLR 2,4&9) ***(Abdulahad et al., 2011).***

There is an association between HMGB1 and autoimmune disorders in which it serves as a significant target antigen. Increased HMGB1 expression has been detected in several autoimmune disorders as systemic lupus erythematosus, rheumatoid arthritis and systemic sclerosis ***(Karin et al., 2005, Yoshizaki et al., 2009).***

Psoriasis vulgaris is considered as a tissue-specific autoimmune disease, so it is possible that HMGB1 may also contribute to the pathogenesis of psoriasis vulgaris ***(Lotze et al., 2005).*** Some studies observed an association between HMGB1 and psoriasis vulgaris and showed the elevated HMGB1 serum levels and altered HMGB1 distribution in lesional skin in patient with psoriasis vulgaris.

No cure is available for psoriasis, but various treatments can help to control the symptoms ***(Johnson et al., 2012).*** Though many treatments are available, psoriasis can be difficult to treat due to its chronic recurrent nature. A new generation of targeted immune therapies is being subjected to more investigation in order to advance treatment option for psoriasis vulgaris.

Aim of the work

The aim of this work is to investigate the role of HMGB1 in the pathogenesis of psoriasis vulgaris by examining the degree of its expression in the tissue of psoriatic patients and its relation to disease severity and the response to NB-UVB phototherapy.

Psoriasis vulgaris

Psoriasis is a genetically determined, immunologically mediated, chronic inflammatory skin disorder that affects 1.5-3% of the population ***(Langley et al, 2005).*** It occurs worldwide, but the incidence is lower in warmer climates. Although rarely life-threatening, psoriasis is a disabling disease of skin and small joints with a social and economic impact, resulting in a severe impairment of quality of life ***(Rosenberger et al., 2007).***

Epidemiology

- **Prevelance:**

In most reviews, the prevalence of psoriasis is said to be 2% of the world's population ***(Raychaudhuri and Farber, 2001).***

However, in the US and Canada, prevalences as high as 4.6% and 4.7% have been reported, respectively. This contrasts with frequencies in Africans, African- Americans, Norwegian Lapps, and Asian of between 0.4% and 0.7% ***(Christophers, 2001).***

- **Incidence:**

The incidence of the disease, that is the number of new cases occurring in a given population in a defined time, has been estimated to be 60 individuals per 100 000 per year ***(Bell et al., 1991).***

A US study suggested that the annual incidence of psoriasis has doubled in the 30 years between 1970 and 2000, although whether this reflects a true change in incidence or changes in diagnosis patterns is unclear ***(Icen et al., 2009)***.

Factors affecting epidemiology:

- **Age of onset:**

The first attack of psoriasis can appear at any age, from infancy to the eighth decade of life. Two peaks in age of onset have been reported: one at 16-22 years of age and a second peak at 50-60 years (Bimodality in psoriasis onset) ***(Swanbeck et al., 1995).***

Those individuals with early onset psoriasis appear, in general, to have more severe disease and are much more likely to have an affected first-degree relative with psoriasis ***(Stuart et al., 2002).***

In approximately 75% of patients, the onset is before the age of 40 years and in 35-50%, it is before the age of 20 years ***(Raychauduri and Gross, 2000).***

Plaque psoriasis is the most frequent form of the disease in children, followed by guttate psoriasis ***(Seyhan et al., 2006).***

- **Sex effect:**

Males and females are equally affected by psoriasis vulgaris. Many studies indicate that age of onset is younger in females ***(Griffiths et al., 2004).***

- **Climate:**

Climate appears to affect psoriasis prevalence, with higher rates recorded in single countries at greater latitudes from the Equator ***(Chandran and Raychaudhuri,* 2009*).***

There is a strong evidence supporting seasonal variation in psoriasis, with 68% of cases first diagnosed in winter and spring months ***(Griffiths et al., 2004).***

- **Genetic factors:**

There is a strong evidence that psoriasis has an important genetic component. The incidence of psoriasis was much greater amongst first and second degree relatives of sufferers than unaffected control subjects ***(Vasku et al., 2013).***

A positive family history has been reported by 35% to 90% of patients with psoriasis. ***(Chandran et al., 2009).***

The molecular genetic basis of psoriasis is complex, with evidence that multiple genes are involved. At least nine chromosomal susceptibility loci have been revealed (PSORS1-9). However, the exact location of PSORS1 gene remains controversial. Furthermore, the penetrance of PSORS1 locus is estimated to be less than 15%, implying that other genetic and/or environmental factors may also contribute to the liability of the disease ***(Christophers and Henseler, 1992).***

The distribution of the lesions, the severity, and the age of onset were similar in the monozygotic twin pairs, whereas these features differed in the dizygotic twin pairs. This observation suggested that genetic factors also play a role in the clinical course of psoriasis***. (Lonntierg et al., 2013).***

Psoriasis has been associated with certain HLA-types (HLA-Cw6, HLA-B13, HLA-B17, HLA Bw57, HLA-DR4), and those with HLA-Cw6 seem to have a 10-fold higher risk to develop the disease ***(Queiro et al., 2014).*** A collaborative genome-wide association study of psoriasis involving thousands of cases and controls revealed association between

psoriasis and seven genetic loci: HLA-C, interleukin IL12B, IL23R, IL23A, IL4/IL13, tumor necrotic factor TNFAIP3, and TNFAIP1 ***(Elder et al., 2010).***

Moreover, a family history of psoriasis, an early-onset of the disease and the presence of HLA-Cw*0602 (the major determinant of phenotypic expression), have been associated to a more unstable and severe clinical course, as compared to those patients with late onset psoriasis and negative for HLA-Cw*0602 ***(Gudjonsson et al., 2006).***

Triggering factors:

Triggering factors, both external (directly interacting with the skin) and systemic, can elicit psoriasis in genetically predisposed individuals ***(Skov and Baadsgaard, 2000).***

❖ External triggering factors:

The Koebner phenomenon is observed in approximately 25% of patients with psoriasis ***(Griffiths et at., 2004).*** Psoriatic lesions can also be induced by many forms of cutaneous injury e.g, trauma, sunburn, morbilliform drug eruption and viral exanthem. ***(Sagi and Trau, 2011).***

❖ Systemic triggering factors:

- **Infections:**

Infections, particularly bacterial infections, may induce or aggrevate psoriasis ***(Van de Kerkhof and Nestle, 2012).***

Streptococcal infections, especially pharyngitis, are the most common offenders ***(Gelfand et al., 2005).*** Human Immunodifficiency Virus (HIV) infection has also been shown to aggravate psoriasis ***(Nestle et al., 2009).***