Transforming Growth Factor Beta 1 gene Polymorphism in Psoriasis Vulgaris among Egyptians

Thesis
Submitted for partial fulfillment of the
MD degree in Dermatology
BY

SAMEH YOUSSEF FAHMY
(M.Sc)
Cairo University

Supervisors

Prof. Dr. Heba Helmi Elhadidi
Professor of Dermatology
Faculty of Medecine
Cairo University

Dr. Akmal Saad Hassan
Assistant professor of Dermatology
Faculty of Medecine
Cairo University

Dr. Ghada Mohamed EL-hanafy
Assistant professor of Dermatology
Faculty of Medecine
Cairo University

Prof. Dr .Khalda Sayed Mohamed
Professor of Molecular Genetics
Molecular Genetic Department
National Research Centre

Faculty of Medecine
Cairo University
2016

Acknowledgement

First, thanks to GOD for blessing this work until it has reached its end, as a part of his generous help throughout our life.

It was an honor to work under the supervision of eminent professors, who lent me their whole hearted support and immense facilities as is their usual with their juniors. To them, I owe more than I can record.

I would like to express my deepest gratitude and highest appreciation to Dr. HEBA EL HADIDI Professor of Dermatology Faculty of Medicine Cairo University for her continuous encouragement, generous support and unlimited help.

I would like to express my deepest gratitude and highest appreciation to Dr. AKMAL SAAD, Assistant Professor of Dermatology, Faculty of Medicine, Cairo University, for his generous support and his great and supreme effort in every part of this work.

I am deeply indebted to Dr. KHALDA SAYED Professor of Genetics, Genetic Department National Research Center for her unlimited effort ,cooperation,effort and useful instructions.

Endless thanks to Dr. GHADA ALHANAFY Lecturer of Dermatology, for her constructive valuable advice and excellent supervision.

I would like to offer my deepest gratitude to all my senior staff, and my colleagues in the Department of dermatology, Cairo University and National Research Center for their help during the preparation of this work.

Finally, I dedicate this work to my loved ones, my family with special dedication to my MOTHER AND FATHER for endless giving and support could never be forgotten or paralleled.

Abstract

Background. Psoriasis is a chronic inflammatory, immune-mediated skin condition characterized by periods of spontaneous remission and exacerbations affecting approximately 2-3% of the population worldwide, TGFβ1 has a conflicting role in pathogenesis of psoriasis as it has been demonstrated to activate angiogenesis and stimulate fibroblasts yet it inhbits keratinocyte proliferation .

Aim of study: To add more insight to the role played by TGFβ 1 in psoriasis, by studying its gene polymorphism in codon 10 in the blood of psoriatic patients. It also aimed to analyze the relationship between TGF-β1gene polymorphism and susceptibility of psoriasis in a sample of Egyptian patients.

Patients and methods: This case control study included 70 patients and 100 controls examined for TGF-β1 gene polymorphism by PCR-RFLP.

Results: Statisticaly significant difference was found between psoriatic patients and control regarding TGF-β1 gene polymorphism at codon 10,morover Statistically significant difference was found between cases with normal genotype and those with polymorphic mutant genotype regarding postive family history of psoriasis (P=0.004),No statistically significant difference was found between cases with normal genotype and those with polymorphic mutant genotype as regard the sex (P=0.50), duration of illness (P=0.57), onset of disease either early or late onset (p=0.051), severity according to PASI score (P=٠.٨٢), associations with psoriatic arthritis(P=0.24) .

Conclusions: Egyptian psoriasis sample patients showed increased TGFβ1 gene polymorphism in the blood compared to controls which prove that the TGFβ 1 gene polymorphism in codon 10 is associated with susceptibility to psoriasis.

Key words: Psoriaisis Vulgaris , TGF-β1 gene polymorphism.

Contents

List of Abbreviations

Ar	:	Argenine
ALK	:	Activin receptor like kinase
AMPs	:	Anti microbial peptides
APCs	:	Antigen presenting cells
BMI	:	Body mass index
BMP	:	Bone morphogenic proteins
C	:	Cytosine
CDK	:	Cyclin-dependent kinase
CDKN2A	:	Cyclin-dependent kinase inhibitor 2A
C T	:	Computed tomography
CCR	:	Chemokine receptors
CLA	:	Cutaneous lymphocyte-associated antigen
CREB	:	C-AMP response element binding protien
CCL	:	Chemokine C-C ligand
CCR	:	Chemokine C-C receptor
CD	:	Clustern of defferntiation
CCHCR	:	Coiled coil helical rod
ESR	:	Erytherocyte sedimentation rate
ECM 1	:	Extra cellular matrix 1
EGF	:	Epidermal growth factor
FOXP3	:	Forkhead box P3
G-CSF	:	Granulocyte colony stimulating factor
GM-CSF	:	Granulocyte-macrophage colony stimulating factor
GF	:	Growth factor
ICAM-1	:	Intercellular adhesion molecule-1
IFNγ	:	Interferon gamma
LFA	:	Lymphocyte functional antigen
Leu	:	leucine
Mhc	:	Major histocompatibilty complex
NK	:	Natural killer cell
NGF	:	Nerve growth factor

PCR	:	Polymerase chain reaction
PDGF	:	Platlet drived growth factor
Pro	:	Proline
PSV	:	Paralogoussequence variant
RFLP	:	Restriction fragment length polymorphism
RT-QPCR	:	Real time-quantitative polymerase chain reaction
STAT	:	Signal transducer and activator of transcription 3
SNP	:	Single nucleotide polymorphism
TNF	:	Tumor necrosis factor
TCR	:	T cell receptor
TCRGR	:	T cell receptor gene rearrangement
TGF-bR1	:	Transforming growth factor beta receptor 1
Th	:	T-helper
TLRs	:	Toll like receptors
TNF-α	:	Tumor necrosis factor-alpha
Tregs	:	T regulatory cells
TGF	:	Transforming frowth factor
UVA	:	Ultraviolet-A
VCAM	:	Vascular cell adhesion molecule
VLA	**:**	Very late antigen
VPF	**:**	Vascular permiabity factor
VEGF	:	Vascular endothelial groth facctor

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Chapter 1

Psoriasis

Psoriasis is a chronic inflammatory, immune-mediated skin condition characterized by periods of spontaneous remission and exacerbations affecting approximately 2-3% of the population worldwide ***(Nickoloff and Nestle, 2004).***Different clinical presentations are present, the most common one is psoriasis vulgaris, which is characterized by sharply demarcated, erythematous, and scaly symmetrical plaques. Histologically, keratinocytes show abnormal differentiation and hyperproliferation, inflammatory infiltrates invade the dermis and the epidermis, and a marked angiogenesis is present ***(Sabat et al., 2007).***

A-Epidemiology

Although psoriasis can begin at any age, epidemiological studies demonstrate that it most commonly occurs between the ages of 15 and 25 years ***(Henseler and Christophers, 1985).*** It has been reported at birth and in people of advanced age. The concept of early and late onset psoriasis was first introduced by Henseler and Christophers in 1985. They reported two clinical presentations of psoriasis, type I and II, distinguished by a bimodal age at onset. Type I begins on or before age of 40 years; Type II begins after the age of 40 years. Type I disease accounts for more than 75% of cases. Patients with early onset, or type I psoriasis, tended to have more relatives affected and more severe disease than patients who have a later onset of disease or type II psoriasis (***Henseler and Christophers, 1985***).

B-Pathogenesis of psoriasis:

The pathogenesis of psoriasis is multifactorial, with genetic, environmental and immunological factors contributing to the phenotype ***(Nakajima, 2012).***

1) Genetic factors

Psoriasis is an immune mediated disease which occurs in genetically susceptible individuals ***(Newman and Weinberg, 2008).*** The role of hereditary transmission in the pathogenesis of psoriasis is still poorly understood. Epidemiologic studies have confirmed that genetic factors are strongly involved in the pathogenesis of this disease and showed that there is a three fold increased risk of psoriasis in monozygotic twins compared to fraternal twins ***(Tonel and Conrad, 2009).*** Several genome-wide association studies have been carried out, 36 susceptibility loci have been identified ***(Tsoi et al., 2012).*** PSORS 1, tightly linked to HLA-Cw6, is the most frequent detected allele ***(Nair et al., 2006).*** This gene may function in antigen presentation via Major histocompatibility complex (MHC) I, which aids in the activation of the overactive T cells characteristic of psoriatic inflammation ***(Newman and Weinberg, 2008).***

Pattern of inheritance in psoriasis:

The contributions of genetic components as predisposing factors for psoriasis are well established. Psoriasis heritability is thought to be up to 90% **(*Liu et al., 2007*).*Farber et al. in 1974*** stated that the child of one psoriatic patient has a 16% chance to develop psoriasis, while if both parents are affected, the risk rises up to 50%.

Svejgaard et al. in 1975reported the increased incidence of psoriasis with human leukocyte antigen (HLA)-B13, HLA-B17, HLA-B37, HLA-Bw16 and HLA-Cw6.

It was reported that there are two types of psoriasis regarding the HLA relation. Type I psoriasis which is hereditary, strongly HLA related, characterized by early onset and severe course. Type II psoriasis on the other hand, is sporadic, HLA unrelated, characterized by late age of onset and mild course **(*Gudjonsson et al., 2002).***

Despite the clear familial aggregation of psoriasis, the precise inheritance model has been under debate. Currently, most investigators agree that psoriasis belongs to the group of complex diseases, the inheritance being multifactorial – genetic variants in multiple genes interact both with each other and the environment. Several disease susceptibility loci have been suggested as predisposing factors **(*Elder et al., 2001).***

Classic genomewide linkage analysis has identified nine locations (loci) on different chromosomes associated with psoriasis. They are called psoriasis susceptibility 1 through 9 (PSORS1 through PSORS9). Within those loci are genes. Many of those genes are on pathways that lead to inflammation. Certain variations (mutations) of those genes are commonly found in psoriasis **(*Nestle et al., 2009).***

The major determinant is PSORS1, which probably accounts for 35-50% of its heritability. It controls genes that affect the immune system or encode proteins that are found in the skin in greater amounts in psoriasis. PSORS1 is located on chromosome 6 in the MHC, which controls important immune functions. Three genes in the PSORS1 locus have a strong association with psoriasis vulgaris: HLA-

C variant HLA-Cw6, which encodes a MHC class I protein,mouse coiled coil alpha helical rod protein(CCHCR1), which encodes a coiled protein that is overexpressed in psoriatic epidermis **(*Nestle et al., 2009*)**.

2) Environmental factors

Psoriasis is triggered by exogenous or endogenous environmental stimuli in genetically susceptible individuals ***(Bowcock and Krueger, 2005).*** Triggers for psoriasis include:

- Alcohol: Alcohol abuse may contribute to the increase of Tumor necrosis factor alpha converting enzyme (TACE) expression and also to the elevated plasma tumor necrosis factor alpha receptor I (TNFRI) concentration in psoriasis patients ***(Serwin et al., 2008).*** In addition, alcohol stimulates the release of histamine and can aggravate skin lesions as a consequence ***(Smith and Fenske, 2000).***
- Smoking: Nicotine can modulate the functional capacity of dendritic cells (DC) and can increase the secretion of pro-inflammatory Th1 cytokines by DC. Additionally, nicotinic cholinergic receptors demonstrated on keratinocytes , stimulate calcium influx and accelerate cell differentiation; they can also control keratinocyte adhesion and upward migration in the epidermis ***(Nouri-Shirazi and Guinet, 2003).***
- Obesity: Circulating levels of TNF-α, soluble TNF-α receptors, and in vitro TNF-α production are all significantly increased in obese patients ***(Tanaka et al., 2001).*** In a case–control study, ***Naldi et al. (2005)*** found that a moderately increased Body mass index(BMI) (26–29) was associated with a slightly increased risk of psoriasis, and clinical obesity (Body mass index) > 29 more than doubled the risk of psoriasis. Further support for a link

between these two conditions comes from the observation that obesity is more prevalent in patients with severe as opposed to mild psoriasis ***(Neimann et al, 2006)*** and an increased prevalence of metabolic syndrome in psoriasis patients has recently been reported ***(Bowcock and Krueger, 2005).***

- Streptococcal throat infection: the onset of guttate psoriasis is often preceded by throat infection with beta haemolytic streptococci ***(Naldi et al., 2001).***
- Stress and Sleep disturbances**:** Sleep disturbance decreases skin barrier function recovery and increases plasma TNF-α ***(Altemus et al., 2001).***
- Drugs e.g. lithium, beta blockers, interferon alpha, withdrawal of systemic corticosteroids,anti-malarial, TNF alfa inhibitors can aggrevate psoriasis ***(Newman and Weinberg 2008).***
- Local trauma (Kobner's phenomenon) and emotional stress, occasionally correlate with the onset or flares of psoriatic lesions ***(Newman and Weinberg 2008).***

3) Immunological factor (immunopathogenesis)

Over the last 20, years it has been continuously discussed whether psoriatic skin lesions arise from a primary alteration in epidermal keratinocytes or in dermal immunocytes. Nowadays, it is believed that psoriasis is most likely a Th1/Th17 induced inflammatory disease (Figure 1 and 2) ***(Coimbra et al., 2012).*** Arguments for considering psoriasis as a T-cell-mediated dermatosis include: 1) Presence of activated T cells in the skin lesions 2) Cure of the disease by bone marrow transplantation from healthy persons and transfer of the disease by transplantation of bone marrow from psoriatic patients 3) Demonstration of the impact of immunocytes by severe combined immunodeficiency mice experiments 4)

Therapeutic effects of immune-suppressants targeting T lymphocytes ***(Schottelius et al., 2004).***

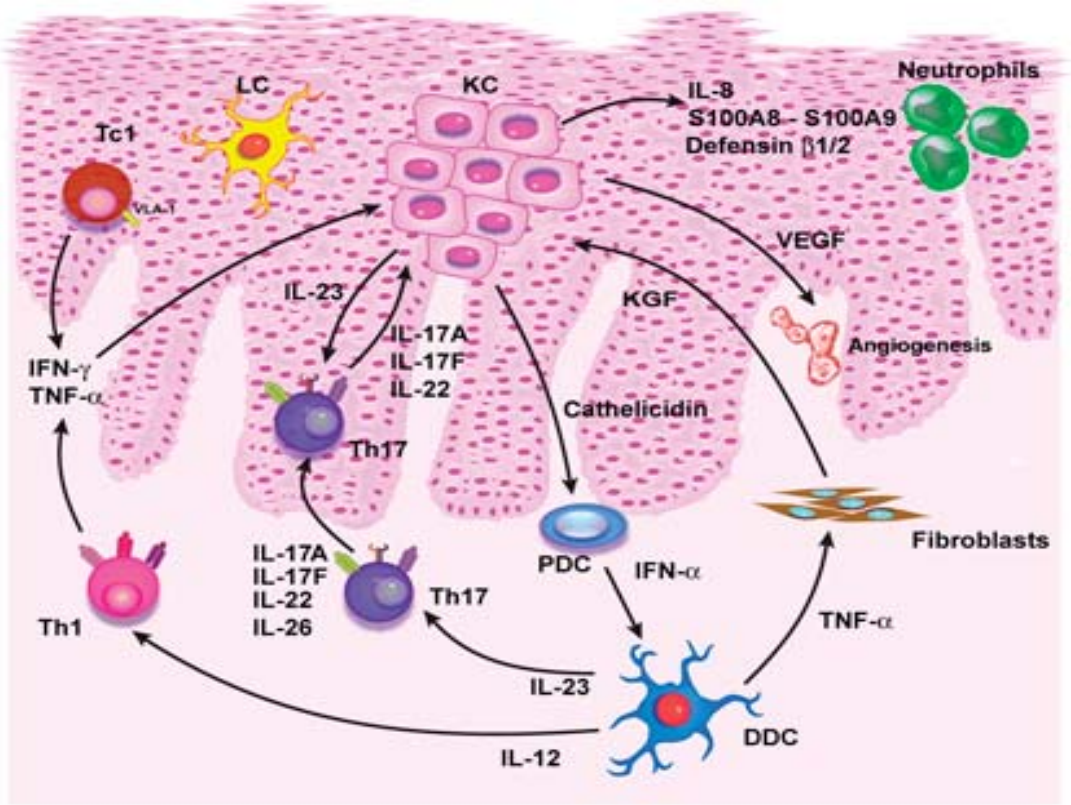

Figure 1: Immunopathogenesis of psoriasis***)*** **in which DDC secretes IL-12,IL 23and TNF alfa which stimulate Th 1,Th 17 , Fibroblasts respectively to produce its mediators to induce psoriasis** DDC: Dermal Dendritic cell, IFN-γ: Interferon gamma, IL: Interleukin, KGF: Keratinocyte growth factor, pDC: Plasmacytoid dendritic cells, Th: T Helper, TNF-α: Tumor necrosis factor α, VEGF: Vascular endothelial growth factor ***(Cesare et al., 2009)***