THE ROLE OF THE INTERLEUKIN 23R GENE POLYMORPHISM IN PSORIASIS

Thesis

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ABSTRACT

Background Psoriasis is a chronic, inflammatory skin disease with approximate 2-3% prevalence in the general population. The etiology of psoriasis is not fully understood, but it appears to be multi-factorial, involving both genetic and environmental influences. Although the precise mechanism by which polymorphisms in *IL23R* influence the disease process still requires further clarification, the associations and functional evidence suggest that the IL23 pathway has a key role in the pathogenesis of psoriasis. **Objective** is to study the role of *IL23R* Arg381Gln SNP rs11209026 and other SNPs (rs2201841) of the IL23R gene in psoriasis in the Egyptian patients. **Methods** This study included 30 psoriatic patients and 30 normal individuals. Real time PCR was carried out for the analysis of rs11209026 SNP while PCR – RFLP was performed for the analysis of IL23R gene SNPs (rs2201841). **Results** Our results revealed that the (G) allele of rs11209026 (IL23R Arg381Gln) is risky while the (A) allele is protective OR 6.510 (95% CI 1. 376 - 30.792).On the other hand, genotyping of rs2201841 showed no significant difference in the 2 studied groups.

Conclusion Association of IL23R Arg381Gln with psoriasis indicates that genes participating in IL23 signaling play a significant role in psoriasis pathogenesis.

Key words: IL23Rgene, SNPs, Psoriasis, PCR-RFLP, Real time PCR

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List Of Abbreviations

HLA	**Human leukocytic antigen**
BAX:	**Bcl-2-associated X protein**
BCL2	**B-cell lymphoma 2**
CCL20	**chemokines ligand 20.**
CCR6,	**Chemokine (chemotactic cytokines) receptor 6**
Cdsn:	***Corneodesmosin***
DCM	**Dilated cardiomyopathy**
DCs	**Dendritic cells**
EGF	**Epidermal growth factor**
GD	**Gravis diseade**
GVHD	**Graft-versus-host disease**
***HCR* protein:**	**Helix coiled-coil rod homologue**
HSCT	**Hematopoietic stem cell transplantation**
IBD	**Inflammatory bowel diseases**
CD	**Crohn's disease**
PB	**Peripheral blood**
K2-EDTA	**Potassium ethylene diamine tetra acetic acid**
ICAM-1	**Inter-Cellular Adhesion Molecule 1**
IL23R:	**Interleukin 23 receptor**
Jak2,	**Janus kinase 2**
JNK.	**c-jun N-terminal kinase**

KCs	**Keratinocytes**
MAPK:	***Mitogen-activated protein kinase***
MMP9	**Matrix metalloprotease**
mRNA	**Messenger RNA**
NK	**Natural killer**
PCR	**Polymerase chain reaction**
RFLP:	**Restriction fragment length polymorphism.**
FRET	**Fluorescence resonance energy transfer**
LC	**Light Cycler® capillary**
Tm	**Melting points**
TBE Buffer	**Tris-borate EDTA buffer**
PKC-alpha	**Protein kinase C-alpha**
PSORS 1-7:	***Psoriasis susceptibility regions 1-7***
SAPK	**Stress-activated protein kinases**
SNP	**Single nucleotide polymorphism**
STATs	**Signal transducers and activators of transcription**
TGF-α	**Transforming growth factor-α**
TLR	**Toll like receptor**
TNF	**Tumor necrosis factor**
TNF-α,	**Tumor necrosis factor-α**
Tyk2,	**Tyrosine kinase 2**
γ-IFN	**Gamma interferon**

INTRODUCTION

The IL23R protein was identified and characterised in 2002. The functional IL23R protein is heterodimeric, comprising the *IL23R* subunit on chromosome 1p31 and an *IL12Rβ1* subunit on chromosome 19p13. The latter subunit is also common to the IL12 receptor which has an *IL12Rβ2* subunit as the second part. The ligand, a proinflammatory cytokine interleukin 23 (IL-23), is also heterodimeric and is composed of a unique p19 subunit (chromosome 12q13) and p40 subunit (chromosome 5q33), which is also a component of IL-12. IL-23 is a pivotal cytokine in the differentiation of T helper cells, especially their differentiation into Th17 T cells ***(Lappalainen, 2008).***

IL-23 signals through a receptor that links to Tyk2 (tyrosin kinase 2) and Jak2 (is a protein Janus tyrosine kinase 2) involved in a specific subset of cytokine receptor signaling pathways. The activation of these intracellular signaling pathways mediates the expression of a variety of genes in response to cell stimuli, and thus plays a key role in many cellular processes such as cell growth and apoptosis ***(Stewart and Trinchier, 2009).***

In response to infection, CD4 helper T (TH) cells differentiate into distinct effector subsets that are characterized by their unique cytokine expression and immune regulatory function. A distinct TH subset, termed TH-17, TH17 or inflammatory TH (THi), has been recently identified as a distinct TH lineage mediating tissue inflammation which is reinforced by IL-23, TH17 cells produce IL-

17, IL-17F and IL-22, all of which regulate inflammatory responses by tissue cells but have no importance in TH17 differentiation ***(Nurieva, 2007).***

The Th17 pathway has generated great interest in diseases of the immune system and is implicated in the pathogenesis of autoimmune disease such as psoriasis. In a study examined skin biopsies of psoriasis lesions, found that Th17 cells, and IL-23 receptor, were present in greater amounts in psoriasis lesions. Interleukin IL 23 stimulates survival and proliferation of Th17 cells, and thus serves as a key master cytokine regulator for these diseases. In psoriasis, IL-23 is overproduced by dendritic cells and keratinocytes. Future targeting of these key cytokines is likely to lead to dramatic clinical improvement in patients with psoriasis ***(Feldman et al., 2008).***

Psoriasis is a common, chronic autoimmune disease of the skin, which affects approximately 2% of the general population. The specific pathogenesis of psoriasis is not completely understood ***(Danilenko, 2008).*** Psoriasis is defined by thickening of the epidermis (acanthosis) due to increased proliferation of keratinocytes, ***(Ma et al., 2008)***

Variations in the IL23R gene have been associated with psoriasis. Each of the known IL23R variations (polymorphisms) changes a single amino acid in the interleukin 23 receptor ***(Capon et al., 2007).***

Studies have shown that single nucleotide polymorphism (SNP) Arg381Gln in the IL23 receptor gene on the chromosome 1p31 is associated with psoriasis ***(Rahman et al., 2008).*** This variation has also been shown to protect against ankylosing spondylitis and Crohn's disease, which are other disorders associated with chronic inflammation (***Capon et al., 2007).***

Aim of the Work:

The aim of this work is to study the role of genetic polymorphism of the IL23 receptor gene in psoriasis in Egyptian population.

PSORIASIS

Importance of the Skin:

The skin is the body largest organ. It forms a physical barrier against the environment, protecting against foreign substances and microorganisms, maintaining water balance and regulating body temperature. The epidermis is the uppermost compartment of the skin, separated from the underlying dermis by the basement membrane (figure1).

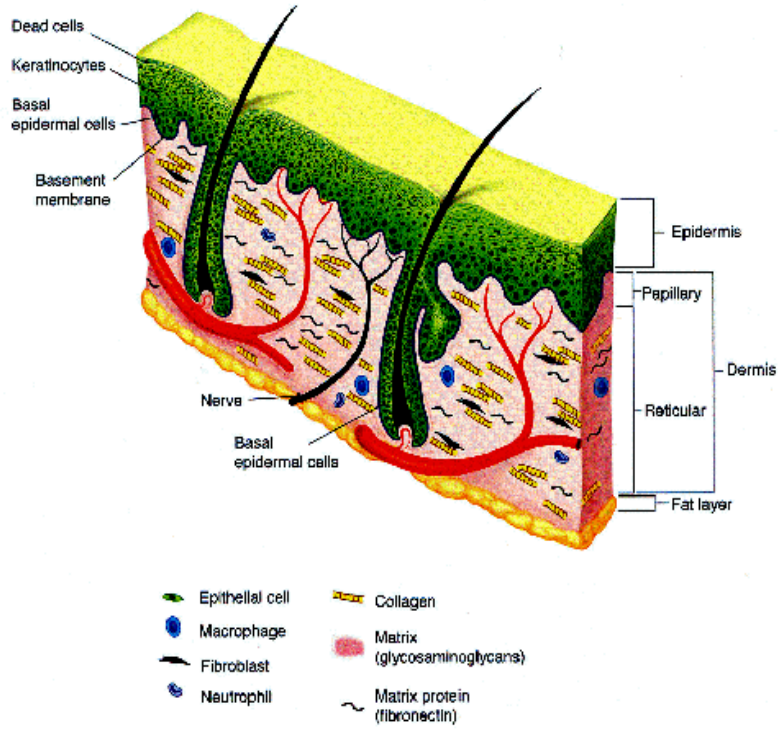

Figure 1: The structure of the normal skin (Carlin L., 2008).

There are two cooperative pathways of immune system that can be mobilized to eliminate foreign antigens, or protect from infectious agents or tumor cells. The innate immune response is fast and acts as a first line of defense against common microorganisms,