Estimation of Toll-like receptors 2,4 & their adapter molecule MyD 88 before & after phototherapy in psoriasis

Thesis

Submitted for fulfillment of M.D. degree in Dermatology

By

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2009

ABSTRACT

Introduction:

Psoriasis is a common and chronic skin disease associated with both genetic and environmental risk factors. Certain microorganisms could induce or exacerbate psoriasis through activation of keratinocyte TLRs (innate immunity).

Toll-like receptors are pattern recognition receptors for conserved molecular patterns of pathogenic microorganisms.When TLR are activated by ligand exposure, TLR may trigger a Myeloid Differentiation Factor 88 (MyD 88) dependent pathway, which end by modulating the expression of many immune response genes.

Patients & methods:

The study included 30 psoriatic patients (plaque type) and 30 controls, patients received 24 sessions of phototherapy (PUVA).Skin biopsies was taken from all the patients(before &after PUVA) & controls and was assessed for TLR 2,4 and MyD88 by PCR.

Results:

Showed significant difference between cases & controls as regards TLR2, TLR4, & MYD88. In addition a significant decrease in all the three studied parameters in patients after phototherapy.

Conclusion:

TLR2, TLR4 and MYD88 may play a role in the pathogenesis of psoriasis. Decrease in the level of these parameters after PUVA may be one of the therapeutic mechanisms of PUVA in psoriasis.

Key words: Psoriasis, toll like receptors 2 &4, phototherapy.

ACKNOWLEDGEMENT

To ALLAH... for helping me a lot in all my life and in this work...

It is a pleasure to express my deepest gratitude to *Dr. Mostafa Mahmoud Abou El Ela,* Professor of Dermatology, Fauclty of Medicine, Cairo University, who very kindly and generously gave much of his time in helping, guiding and advising me.

I 'm also grateful to *Dr. Noha Abd El Rehim Nagui* , assistant professor of Dermatology, Faculty of Medicine, Cairo University, for her great help, kind supervision and continuous support.

I would like also to thank Dr. *Nermin Eleishi* assistant professor of Dermatology, Faculty of Medicine, Cairo University for her cooperation in the study.

I would like to thank *Dr Laila Ahmed Rashed,* Assistant professor of Biochemistry, Faculty of Medicine, Cairo University, for her kind help in fulfilling the practical aspect of the study.

I would like also to thank Dr. *Rehab Mohamed Sobhi,* Lecturer of Dermatology, Faculty of Medicine, Cairo University, for her interest , guidance and critical review.

Furthermore I would to thank *Dr. Dalia Ahmed Mohamed* Assistant professor of community, Faculty of Medicine, Cairo University, for carrying out statistical analysis of this work.

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List of Abbreviations

- APC: antigen-presenting cell.
- DC: dendritic cell.
- DD: death domain.
- GN: gram-negative.
- HSP: heat-shock protein.
- IFN: interferon.
- Ig: immunoglobulin.
- IL : interleukin.
- IRAKs : IL-1RI-associated protein kinases.
- IRF: interferon regulatory factor.
- JNK: Jun NH_2-terminal kinase.
- LP: lipoprotein.
- LPS: lipopolysaccharide.
- LRR: leucine-rich repeat.
- MAL: myeloid differentiation factor 88 adaptor-like protein.
- MAPK: mitogen-activated protein kinase.
- MyD 88: Myeloid Differentiation Factor 88.
- NF-κB: nuclear factor-κB.
- NK: natural killer.
- PAMP: pathogen-associated molecular patterns.
- PASI : Psoriasis Area Severity Index.
- PG: peptidoglycan.
- Poly-I: C: copolymer of polyinosinic and polycytidylic acids.

- PRR: pattern recognition receptors.
- PUVA: Psoralen and Ultraviolet A
- TAB: transforming growth factor binding protein.
- TAK: transforming growth factor activated kinase.
- TGF: transforming growth factor.
- T_H: T-helper (or helper T).
- TICAM-1: Toll–interleukin 1–containing adaptor molecule-1.
- TIRAP: Toll–IL-1 receptor domain–containing adaptor protein.
- TLRs : toll like receptors
- TNF: tumor necrosis factor.
- Tregs : T regulatory cells.
- TRIF: Toll–IL-1 receptor domain–containing adaptor–inducing interferon-β.
- VEGF: vascular endothelial growth factor.

Introduction

Invading pathogens are controlled by the innate and adaptive arms of the immune system. Adaptive immunity which is mediated by B and T lymphocytes recognizes pathogens by rearranged high affinity receptors. However the establishment of adaptive immunity is often not rapid enough to eradicate microorganisms as it involves cell proliferation, gene activation and protein synthesis. More rapid defense mechanisms are provided by innate immunity, which recognizes invading pathogens by germ-line-encoded pattern recognition receptors (PRR). Recent evidence shows that this recognition can mainly be attributed to the family of Toll-like receptors(TLR). Binding of pathogen-associated molecular patterns (PAMP) to TLR induces the production of reactive oxygen and nitrogen intermediates (ROI and RNI), pro-inflammatory cytokines and upregulates the expression of co-stimulatory molecules, subsequently initiating the adaptive immunity ***(Werling and Jungi 2003).***

Toll-like receptors are pattern recognition receptors for conserved molecular patterns of pathogenic microorganisms. TLRs are found throughout evolution, from Drosophila to humans. In humans, there are 10 TLRs (TLR 1-10), each activated by a different microbial component, but triggering a common signaling cascade leading to the production of inflammatory cytokines ***(Medzhitov 2001 and Takeda et al, 2003).***

TLRs are transmembrane proteins with the extra cellular portion composed of leucine-rich repeats, whereas the intracellular portion shares homology with the cytoplasmic domain of the IL-1 receptor. When TLR are activated by ligand exposure, the intracellular domain of the TLR may trigger a Myeloid Differentiation Factor 88 (MyD 88) dependent pathway that ultimately leads to the nuclear translocation of the transcription factor NFkβ which then acts to modulate the expression of many immune response genes ***(Takeda et al, 2003).***

Psoriasis is a common and chronic skin disease associated with both genetic and environmental risk factors ***(Bowcock et al, 2001)***. There is a growing interest in the role of innate and adaptive immunity in inflammatory diseases such as psoriasis ***(Nickoloff 1999, Aractingi et al, 2001)***. It is conceivable that certain microorganisms could induce or exacerbate psoriasis through activation of keratinocyte TLRs (innate immunity), leading to the secretion of cytokines which activate the acquired immunity via effects on T cells, antigen presenting cells and endothelial cells ***(Rottman et al, 2001).***

It was found that monoethyl fumarate which is succesfuly used in the treatment of psoriasis, interferes with TLR signaling. In addition systemic and topical retinoids which play an important role in psoriasis therapy, have an inhibitory effects on TLR2 ***(Gaspari 2006).***

Curry et al, (2003) reported that Heat Shock Proteins (HSPs) which are already over expressed in psoriatic lesions interact with TLR4 on APCs leading to TNFα and IL-12 secretion thus contributing to psoriasis immunopathology.

Epidermal hyperplasia and follicular hyperkeratosis secondary to IL-8 production have been noted in psoriatic skin ***(Gillitzer et al,1991)***. The microbial compound-induced increase in IL-8 gene expression could be inhibited by anti-TLR2 and anti-TLR4 neutralizing antibodies, suggesting that TLRs are involved in the pathogen-induced expression of this pro-inflammatory cytokine ***(Curry et al, 2003).***

Lastly, it has been found that TLR agonist "Imiquimod" aggravate psoriatic lesions when applied topically ***(Gilliet et al, 2004).***

Aim of the work:

Based on the above mentioned findings, this study aims to detect a possible role of TLRs 2, 4 & their adapter molecule MyD 88 in the pathogenesis of psoriasis and to evaluate if phototherapy has an effect on the expression of these parameters.