Expression Of TLR 2 And 4 And The Detection Of HHV6,7 In Cutaneous lesions of Pityriasis Rosea

Thesis

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بسم الله الرحمن الرحيم


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List of abbreviations

- AD: Atopic dermatitis.
- AP-1: Activator protein1.
- BCG: Bacillus Clamette- Guerin.
- CMV: Cytomegalovirus.
- CpG: Deoxycytidylate-phosphate deoxyguanylate.
- DCs: Dendritic cells.
- DNA: Di-ribo nucleic acid.
- dsRNA: Double stranded ribonuclic acid,
- EBV: Epstein Bar virus.
- ECD: Pathogen binding ectodomain.
- ERK: Extracellular-signal-regulated kinase.
- Env: Envelope protein.
- GN: Gram -ve.
- HHV: Human herpes virus.
- HMCV: Human cytomegalovirus.
- HSCT: Hematopoietic stem cell transplatation.
- HSV: Herpes simplex virus.
- IL-1: Interlukin 1.
- INF: Interferone
- iNOS: inducible nitirc oxysynthase enzyme.
- IP10: INFγ-induced protein 10.
- IRAK: IL1 receptor-associated kinase.

- IRF: INF regulatory factor.
- JNKs: c-Jun-N-terminal kinases.
- KSHV: Kaposi's sarcoma-associated herpes virus.
- LPS: Lipopoly saccharides.
- LRRs: Leucin-rich repeats.
- MAPKs: Mitogen-activated protien kinase.
- MyD88: Myloid differentiation factor 88.
- MMTV: Mouse mammary tumor virus.
- NEMO: NF κB-Essential Modulator
- NFκB: Necrosis factor kappa B.
- OPGL: Osteoprotegrin- ligand.
- PAMP: Pathogen associated molecular pattern.
- PBMCs: Peripheral blood mononuclear cells.
- PCR: Polymerase chain reaction.
- PRR: Pattern recognition receptor.
- PR: Pityriasis rosea.
- TAB: TLAK binding protein.
- TAK1: TGF-activated kinase1.
- TGF: Tumor growth factor.
- TIR: Toll Interlukin1 receptor.
- TNF: Tumor necrosis factor.
- TRAF: TNF receptor-associated factor.
- TRIF: TIR domain-containing adaptor inducing INF-β.
- TIRAP: TIR domain-containing adaptor protein toll domain containing adaptor molecule.

- TICAM: (TRIF)-TIR domain adaptor molecule
- TRIP: TIR-containing adaptor.
- VACV: Vaccinia virus.
- VZV: Varicella zoster virus.

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Abstract

Pityriasis rosea (PR) is a common papulosquamous skin disease in which infective agent may be implicated. Reactivation of human herpes virus 7 (HHV-7) and, in some cases human herpes virus 6 (HHV-6) was suggested to occur in PR. The aim of this study is to detect the possibility of HHV 6,7 involvement in the pathogenesis of PR and it's relation with TLRs 2,4. In our study 25 PR patients, and 25 healthy controls were recruited, a skin biopsy from PR lesions was obtained and real-time PCR was performed to measure HHV6,7 loads as well as TLRs 2,4 levels . Our results indicated a significant elevation in TLR2,4 in our cases as well as a significant elevation HHV6,7 loads .Furthermore, we detected a significant elevation TLR 2,4 in HHV7 positive cases. Our results concluded that TLR 2,4 are involved in viral diseases particularly HHVs, and supported the possibility that HHV7 and to a lesser extent 6 are involved in the pathogenesis of PR.

Introduction

Pityriasis rosea (PR) is a self limited inflammatory condition of the skin that mostly affects healthy children and adolescents **(Amer et al., 2007)**. It classically begins by a herald patch (the mother patch), and is typically asymptomatic after several days it's followed by the appearance of similar smaller lesions on the trunk **(Wolff et al., 2008).**

Numerous studies over the past 50 years have considered various pathogens as potential etiologic agents of PR **(Wolff et al., 2008).** Many studies were focused on the strong possibility that PR is a viral xanthem **(Drago et al., 2006).** These possibilities were based on many symptoms and signs including: the rare recurrence of PR that suggest a lifelong immunity after one episode, the occurrence of seasonal variation in some studies, the clustering in some communities, as well as the appearance of flu-like symptoms in a subset of patients **(Watanabe et al., 2002).**

Many PR etiologic and pathogenic studies have been focused on two particular human herpes viruses (HHVs), human herpes virus 6 and 7 (HHV-6, HHV-7) **(Drago et al., 1997, Watanabe et al., 1999, and Watanabe et al., 2002).**

Toll-like receptors (TLRs) are important pattern recognition receptors. They are considered key molecules of the innate immune system **(Takeda et al., 2003).** A subset of TLRs recognize components of microorganisms and then signaling cascade begins ending by inflammatory cytokine release and gene products that modulate innate immune response, and further instruct development of antigen-specific acquired immunity **(Takeda& Akira, 2005).**

There have been many reports providing evidence that TLRs not only play an important role in immune response in the skin, but also in pathohysiology of numerous inflammatory skin diseases **(McIntruff et al., 2005 and Kang et al., 2006).** TLRs were found to be expressed by keratinocytes which were reported to express TLRs 1, 2, 3, 4, 5, 9, and 10 **(McInturff et all, 2005 and Hari et al., 2010).** Dendritic cells (DCs), and Langerhans cells were also reported to express significant levels of TLRs 2, 3, 4, 8, and 10 **(Renn et al., 2006)** .

TLR2 recognizes a variety of microbial components. These include lipoproteins/lipopeptides from various pathogens **(Takeda et al., 2003).** Studies have reported that TLR-herpes virus interaction occurs when virions engage surface TLR2 on DCs and macrophages, which result in the secretion of inflammatory cytokines by a TLR2-dependant manner **(Sato et al., 2006).** TLR2 has also been implicated in the host immune response to primary herpes simplex virus (HSV-1) infection **(Kurt-Jones et al., 2004).**

It has been reported that cell surface TLR2 and TLR4 recognize viral glycoproteins present on virions, hence, there are many evidences that TLRs have an important role in viral pathogen associated molecular pattern (PAMP)-induced gene induction which leads to activation of host innate immune responses **(Sinead et al., 2006).** Also it has been reported that HHVs alter the regulation of innate immunity as well as adaptive immunity **(Murakami et al., 2010).** In the light of these facts, and as HHV 6, 7 are particularly suspected to be involved in the pathogenesis of PR it seems important to clarify the effects of HHV infection on the TLRs in PR patients.

Aim of the work:

The aim of this work is to show the relation of TLR 2 and TLR4 receptors in patients with PR to detect any possibility of being induced by viral infection with HHV6 and or HHV7 viruses.