



TOLL LIKE RECEPTORS ROLE IN DERMATOLOGY- A REVIEW ARTICLE

Dr. Geeta Kiran Arakkal, Dr. Sudha Vani Damarla, Dr. Harish Kumar Kasetty and Dr Sudha Rani Chintagunta

Dr. Geetakiran Arakkal is Professor and HOD, Dept. of DVL, Gandhi Medical College, Hyderabad.

Dr. Sudha Vani Damarla is Asst. Professor, Dept. of DVL, Gandhi Medical College, Hyderabad.

Dr. Harish Kumar Kasetty is Senior Resident, Dept. of DVL, Gandhi Medical College, Hyderabad.

Dr. Sudharani Chintagunta is Asst. Professor, Dept. of DVL, Gandhi Medical College, Hyderabad.

***Corresponding Author: Dr. Geeta Kiran Arakkal**

Professor and HOD, Dept. of DVL, Gandhi Medical College, Hyderabad.

Article Received on 03/10/2016

Article Revised on 23/10/2016

Article Accepted on 13/11/2016

INTRODUCTION

Toll-like receptors are a class of proteins that play a major role in the innate immune system which is the first line of defence. Toll receptors were identified first in the fruit fly *Drosophila* by Christiane Nüsslein-Volhard in the year 1985.^[1] Toll is a German word, which means “fantastic.” The name “Toll-like receptors” in other species were derived from the similarity to Toll receptors identified in *Drosophila* flies.^[2] Nearly 13 members of the Toll-like receptor families have been identified in human and mice out of which Toll-like receptors 1, 2, 4, 5, 6 and 11 are present on the cell surface and Toll-like receptor 3, 7, 8 and 9 are localized in the endosomal/lysosomal compartment.^[3]

Toll-like receptors (TLRs) are a type of pattern recognition receptors (PRRs) which recognize molecules shared by pathogens which are referred to as pathogen associated molecular patterns (PAMPs). For example, lipopolysaccharide is recognized by Toll-like receptor 4, double-stranded RNA by Toll-like receptor 3 and single stranded RNA by Toll-like receptor 7.^[4,5] The microbial components are identified from the self for immune activation.^[6,7]

Toll-like receptors are found on the surface of immune phagocytic cells such as monocytes, granulocytes, macrophages, dendritic cells and keratinocytes.^[4] The set of expression of Toll like receptors is specific and unique for each cell of the immune system. Keratinocytes have Toll-like receptors 1 to 6 and 9.^[8] Langerhans cells express all Toll-like receptors particularly 1, 2, 3, 5, 6 and 10.^[6] In addition, Langerhans cell produces interleukin-10, a Th2 cytokine suggesting a role in immune tolerance.^[9] Similarly melanocytes have Toll-like receptors 2, 3, 4, 7, 9 and respond to Toll-like receptor 4 ligands by matrix metalloproteinase induction.^[10,11]

TLR Signalling Pathway

Toll-like receptors play a major role in innate and adaptive immunity. Toll-like receptors consist of an ectodomain made of leucine rich repeats that bind the ligands directly.^[2] In addition, accessory molecules also play a role in ligand binding in TLR 4, CD14 and MD2 for the recognition of lipopolysaccharides.^[12-14]

TLR signaling occurs through two different pathways of which one is dependent on universal adaptor protein myeloid differentiation factor 88 (MyD88) and other is independent of MyD88 confined to TLR3 and 4.^[15]

Toll-like receptor signaling pathway initiate with intracytoplasmic Toll/interleukin-1 receptor (TIR) domains which exist in all Toll-like receptors. Toll-interleukin 1 receptor domain-containing adaptors such as MyD88, Toll like receptors adaptor protein (TRAP) and Toll-interleukin1 receptor adaptor-inducing interferon-beta (TRIF) modulate Toll-like receptor signaling pathways. Myeloid differentiation factor 88 is crucial for the induction of inflammatory cytokines triggered by all Toll-like receptors. In the MyD88-dependent pathway, TRAP is specifically involved through Toll-like receptor 2 and 4, whereas TRIF is implicated in the Toll-like receptor 3 and 4 mediated MyD88-independent pathway.^[3] There is activation of nuclear factor kappa B (NF-κB) and other kinases in the MyD88 dependent pathway.^[16,17] Nuclear factor kappa B on activation and along with phosphorylation of p38 mitogen-activated protein kinases (MAPKs) translocates into the nucleus and acts as a transcription factors. These transcription factors release inflammatory cytokines by activating the proinflammatory genes.^[6,18-20] [Figure -1]

The activation and inhibition of Toll-like receptors is influenced by microorganisms and medications. Toll-like receptor ligands trigger a Th1 response to viral, bacterial or fungal antigens and Th2 response to antigens such as

helminthes.^[14] Innate immune response activated by Toll-like receptors further contributes to enhance adaptive response by activating leukocytes, phagocytes and antigen presentation to finally eliminate the pathogens. However, *Yersinia* species and poxviruses may act as Toll-like receptor antagonist by evading host immune response leading to infection.^[18,19] A study by Schnare *et al.* found that the absence of adaptor protein MyD88 gave rise to defective antigen specific Th1 helper cells but a normal Th2 response.^[14,21] Any defects or mutations in Toll-like receptor molecules or the signaling pathway leads to host susceptibility to infections and inflammatory conditions^[6,18,22,23,24,25,26] [Table 1].

Acne vulgaris

Key TLRs: 2,4

Acne vulgaris is a disorder of pilosebaceous duct with various etiological factors. The Gram-positive *Propionibacterium acnes* which colonize the sebaceous follicles produce low molecular chemotactic factors particularly interleukin-8 which draw neutrophils into the lumen of the sebaceous gland. C5a released through the activation of classical and alternate complement pathway is responsible for the secretion of proinflammatory cytokines tumor necrosis factor alpha, interleukin-1 beta and interleukin-8 by monocytes. Peptidoglycan which is the key component of the cell wall of *P.acnes* acts as a ligand for Toll-like receptor 2, which are expressed on peribulbar and perifollicular macrophages.^[27] It is also been shown that the number of cells expressing Toll-like receptor 2 is high in severe acne.^[27] The production of inflammatory cytokines (interleukin-6, interleukin-8, interleukin-12) is proportionate to the interaction of *P. acnes* and Toll-like receptor 2.^[27]

Studies have also identified the role of Toll-like receptor 4 in acne. The lipopolysaccharides in the cell wall of *P. acnes* activates Toll-like receptor 4 resulting in immune and inflammatory responses leading to acne.^[6,18-21,28]

Atopic dermatitis

Key TLRs: 2,6,9

Atopic dermatitis is a chronic inflammatory disease marked by recurrences.^[29] There is a Th2 cytokine immune response and the keratinocytes secrete chemokines attracting eosinophils and Th2 cells. These patients are more prone for bacterial, viral and fungal infections. 90% of atopic dermatitis patients have *S. aureus* in their lesional and healthy skin and is the cause for a frequent flare up of atopic eczema.^[18,30,31] The increased sensitivity to various infections is partly due to diminished amount of antimicrobial peptides such as beta-defensin 1 and 2, cathelicidin (LL-37) and dermcidin. Defects in Toll-like receptors or signaling pathways have also been identified.

Pathogenic organisms express microbial products that activate Toll-like receptor 1, 2, 6 and 9. A strong relationship between severe atopic dermatitis and Toll-like receptor 2 is noticed in some people.^[32,33]

In severe atopic dermatitis patients, single nucleotide polymorphism R753Q in Toll-like receptor 2 allele has been found to be associated with *S. aureus* infection.^[34,35] Polymorphism C-1237T in Toll-like receptor 9 gene has been assigned as the cause for deterioration of immunity in atopic individuals.^[36] These studies show that there is a fault in Toll-like receptor 2/9 which may be genetic dysfunctional proteins or attenuation of a regulatory pathway.^[36-38]

In atopic dermatitis, there is a defective barrier function, receptor expression and signaling pathways results in abnormal cytokine production.^[39-42] Specific therapy with calcineurin inhibitors gives better response in atopic dermatitis by regulating T cells.^[42-44]

Phototherapy with ultraviolet A and ultraviolet B have been found to be effective in atopic dermatitis which acts by altering the immunity and inflammation.^[45-48] In immunosuppression seen in phototherapy is due to cytokine production as a result of stimulation of Toll-like receptor 2 and 4 along with T regulatory cells.^[48]

Allergic contact dermatitis

Key TLRs: 2,4,9

Depending on the Toll-like receptor 2, 4 and 9 signaling a specific autoreactive CD8 response occurs in epidermis when bacterial infections and allergens activate dendritic cells.^[49] Direct activation of the Toll-like receptor 4 is seen in nickel induced inflammatory response.^[50]

Psoriasis

Key TLRs: 1,2,4,5 and 9

Psoriasis is a chronic inflammatory condition of the skin, characterized by altered proliferation and differentiation of keratinocytes and increased antigen presentation, Th1 and Th17 cytokine production in a genetically predisposed individual. There is altered self-recognition of nucleic acids and interferon- γ and beta produced by plasmacytoid dendritic cells that express intracytoplasmic Toll-like receptor 7 and 9.^[51] Plasmacytoid dendritic cells constitute 16% of the cell population in the dermal infiltrate in psoriasis which is not common in atopic dermatitis and is not seen in the normal skin.^[51]

Psoriatic plaques are resistant to pathogens like *S. aureus* due to the high levels of antimicrobial peptides in psoriatic skin unlike atopic dermatitis which is a Th2 mediated condition. Psoriatic skin express high levels of Toll-like receptors 1, 2, 4, 5 and 9 which when stimulated are responsible for resistance to pathogenic organisms. The role of yeast *malassezia furfur* in the development of psoriatic scalp lesions is found to be due to up regulation of Toll-like receptor 2 and mRNA expression in human keratinocytes. Anti-Toll-like receptor 2 antibodies inhibit human beta defensin-2 and interleukin-18 gene expression.^[6,18,19,28]

On the contrary, Toll-like receptor activation has also been found to have exaggerated psoriasis when Toll-like receptor 7 were activated by the topical application of imiquimod which is a topical agonist.^[51,52] The possible autoimmunity in psoriasis may be due to antimicrobial peptide cathelicidin (LL-37) which present self-DNA to activate Toll-like receptor 9 on plasmacytoid producing interferon α . Use of topical and systemic retinoids control psoriasis by downregulating Toll-like receptor 2.^[48] Fumaric acid ester is used as an immunotherapy in psoriasis which inhibits nuclear factor kappa B activation by interfering with lipopolysaccharide signaling via Toll-like receptor 4 in the dendritic cell. This in turn decreases interleukin 12p70 and interleukin-10 production and modulates dendritic cell polarization.^[53] Salicylates and parthenolide (nonsteroidal anti-inflammatory drugs) block I κ B kinase activity which are part of Toll-like receptor signaling cascade.^[54,55] Although several clinical drug trials targeting the common signaling pathways of Toll-like receptor super family to prevent p-38 mitogen-activated protein, nuclear factor kappa B activity and tumor necrosis factor production, precaution must be taken while assessing Toll-like receptor therapies.^[55]

Skin infections

When confronted with *Staphylococcus aureus* or *Candida albicans*, human keratinocyte signal through TLR2.^[8,16] The stimulated keratinocytes via the nuclear factor kappa B controlled genes release interleukin-8, nitric oxide and chemokines.^[16] Ligands 2, 3 and 5 stimulate matrix metalloproteases (MMPs)1 and 9 with pathway regulating NF- κ B inflammation, cell migration and wound healing.^[17] Translocation of NF- κ B with activated keratinocytes stimulates dendritic cell maturation and antigen presentation.^[22] The cytokines released mobilise leukocytes and other killer cells.^[8]

Staphylococcus aureus

Key TLRs: 2,6

The skin and mucous membranes are colonized by *S. aureus* in 20% of the human population. Infections such as impetigo, folliculitis, furuncle, carbuncle, cellulitis, sepsis, endocarditis and bacteremia are caused by these organisms. Lipoproteins, peptidoglycans and lipoteichoic acids are the components of bacteria acting as an agonist to LR 2/6 or Toll-like receptor 2/2. The key adapter molecule myeloid differentiation factor 88 is activated by Toll-like receptor 2 and interleukin-1R leading to upregulation of human beta defensin 3 contribute to the immune response against *S. aureus*. Interleukin-1R seems more relevant than Toll-like receptor 2 in host immune response to *S. aureus*.^[6,18,19]

Candida albicans

Key TLRs: 2,4

C. albicans is a dimorphic fungus causing mucocutaneous infections leading to morbidity and mortality in the immunocompromised. Toll-like receptor 2 and 4 are involved in signaling cascades induced by *C. albicans*. The surface of yeasts contains several

carbohydrates such as glucans, mannans and chitin eliciting host immune response. Toll-like receptor 2 identifies phospholipomannan while O-bound mannan is recognized by Toll-like receptor 4. Activation of Toll-like receptors by *C. albicans* results in the production of cytokines and recruit inflammatory mediators to the site of infection. *C. albicans* is found to manipulate Toll-like receptors in order to perpetuate infections in vulnerable individuals.^[6,19]

Dermatophytosis

Reduced expression of TLR4 observed in dermatophytic lesions is responsible for decreased inflammatory response which recognizes bacterial and fungal elements.^[56]

Herpes viridae infection

Key TLRs: 2,3,9

Host immune response in herpes simplex virus and varicella zoster virus is mediated by Toll-like receptor 2, 3 and 9. Patients with Toll-like receptor 2 abnormalities in genital herpes simplex virus infections have more viral shedding and repeated episodes. Toll-like receptor 3 deficient people are prone to herpes simplex virus encephalitis.

Leprosy

Key TLRs: 1,2

Leprosy is a chronic mycobacterial disease caused by *Mycobacterium leprae* and the diagnosis is based on the clinical, histopathological and immunological spectrum. When the host immunity is good leprosy is manifested by cell mediated immunity Th1 cytokines (interferon gamma, interleukin-12, interleukin-18) and develop tuberculoid form. While the immunity is low host immune response is seen with Th2 cytokines (interleukin-4, interleukin-10) and this enhances humoral immune response resulting in lepromatous leprosy. Lipoproteins 19 and 33 kDa from *M. leprae* mediate cellular activation of monocytes and dendritic cell through Toll-like receptor 2/1. Incubation of 19 kDa with antipsychotic drug in the presence of Th1 cytokines produced tumor necrosis factor alpha.^[57] There is a strong upregulation of Toll-like receptor 1 by interferon alpha. Conversely, tumor necrosis factor alpha production is inhibited by Th2 cytokines. The antigen presenting cells from tuberculoid lesions express Toll-like receptor 1 more than lepromatous lesions. Hence, the activation of Toll-like receptor 1 and Toll-like receptor 2 may be important for the host defence against *M. leprae*.^[27] The activation of Toll-like receptor 2 on the surface of Schwann cells with 19 kDa lipoprotein increases the apoptotic Schwann cells and this may be responsible for the nerve damage in leprosy.^[6,18,19,28]

Syphilis

Key TLRs: 2,5

Syphilis is a sexually transmitted disease caused by the spirochete *Treponema pallidum*. The lipopeptides present on the surface of *T. pallidum* acts as a ligand for

Toll-like receptor 2 on dendritic cells participates in the adaptive immune response through T-cell activation and Th1 cytokine release. Exposure of immature dendritic cells to anti Toll-like receptor 2 antibodies led to inhibition of *T. pallidum*, expression of dendritic cell surface maturation markers and inhibition of T-cell activation. Flagellin, a key component of flagellum bind to Toll-like receptor 5 and activate nuclear factor kappa B through myeloid differentiation factor 88 dependent pathway leading to the production of cytokines such as tumor necrosis factor alpha.^[19]

Nonmelanoma skin cancers

Key TLRs: 1,2,3,5,6,7,8

The most common nonmelanoma skin cancers are basal cell carcinoma and squamous cell carcinoma. Increased expression of Toll-like receptors 1, 2, 3, 5, 6, 7, 8 is seen in squamous cell carcinoma, whereas interferon gamma in the basal cell carcinoma. Topical application of the imiquimod in basal cell carcinoma led to induction of specific subset of dendritic cells which mediate destruction of basal cell carcinoma lesions and in squamous cell carcinoma Toll-like receptors 7 and 8 are manipulated to activate proinflammatory cytokines against squamous cell carcinoma. A synthetic CpG-ODN targets Toll-like receptors 9 and is considered in treating basal cell carcinoma.^[27-58, 59]

Melanoma

Key TLRs: 4,7,9

Exposure to ultraviolet radiation is the main risk factor for melanoma. Tumor progression in melanoma is by activating matrix metalloproteases and cytokine production through Toll-like receptor 4 signaling. Different Toll-like receptor 9 agonists are now included in vaccine formulations for human trials as Toll-like receptor 9 on melanocytes are found to alter the immune response.^[60] Toll-like receptor 7 has immunomodulating effect, which can be used as immunotherapy against melanoma.

Wound healing

Key TLRs: 2,3,4,9

In the normal human skin Toll-like receptors 2, 3, 4 are present in keratinocytes, Langerhans cells, fibroblasts, immune cells and mast cells in the dermis, as well as endothelial cells of the skin microvasculature.^[61] After epidermal damage or microbial infection, Toll-like receptor 9 messenger RNA expression increases suggesting that Toll-like receptor 9 derives from infiltrating peripheral blood mononuclear cells.^[62] The findings of increased Toll-like receptor 4 expression in fibroblasts isolated from hypertrophic scars and concomitant upregulation of myeloid differentiation factor 88 expression, prostaglandin E2, interleukin-6, interleukin-8 and monocyte chemoattractant protein-1 when compared with normal skin tissue propose the role of Toll-like receptor in dermal component of wound healing.^[63,64] Cutaneous injury upregulates Vitamin D3 generation in keratinocytes which in turn increases Toll-

like receptor 2 expression. Skin injury leads to infiltration of plasmacytoid dendritic cells in the wounds. These plasmacytoid dendritic cells acknowledge self-nucleic acids released by damaged cells in the skin wounds by producing interferon alpha/beta through Toll-like receptors 7 and Toll-like receptor 9.^[65] Hence, Toll-like receptor expression and activation have a role in wound healing.

Autoimmune disorders

Key TLRs: 3,4,7,8,9

Toll-like receptors 3,4,7,8 and 9 are involved in the pathogenesis of systemic lupus erythematosus. Defects in the induction of apoptosis and clearing immunostimulatory cell debris, abnormal activation of T-cell and B-cell receptors induce systemic lupus erythematosus.^[66-68] In Sjogren's syndrome there is an upregulation of Toll-like receptor 8, mRNA and ribonucleoprotein stimulated Toll-like receptor 8 signaling similar to systemic lupus erythematosus [Table 2]. TLR3 and TLR4 which are demonstrated on rheumatoid synovium plays a role in autoimmunity in rheumatoid arthritis.

Therapeutic Implications

Several agents function as Toll-like receptors agonists when used as immune and anti-inflammatory medications for viral infections and skin cancer. (e.g.,: Imiquimod and resiquimod are Toll-like receptors 7/8 agonists).^[19,23] Toll-like receptors antagonism is the other strategy of treatment in conditions such as rheumatoid arthritis, systemic lupus erythematosus and septic shock.^[24]

Imiquimod is the first drug to be approved as Toll-like receptor agonist for the treatment of genital warts in humans caused by human papilloma virus.^[23] Imiquimod and imidazoquinolines act by inducing nuclear factor kappa B and proinflammatory cytokines such as interferon alpha, interferon gamma, interleukin-6, interleukin-8 and interleukin-12 by stimulation of myeloid differentiation factor 88 dependent Toll-like receptor 7 signaling pathway. This results in the maturation of naive lymphocytes towards Th1 type. In addition, imiquimod helps Langerhans cell to migrate to lymph nodes enhancing antigen presentation. Imiquimod is approved for the treatment of superficial basal cell carcinoma and actinic keratosis due to its anti-tumoral activity.^[69,70] The other off-label indications are Bowen's disease, lentigo maligna, cutaneous T-cell lymphoma, verruca vulgaris, verruca plana, molluscum contagiosum and verruca plantaris. Imiquimod in a concentration of 3.75% has been approved by Food and Drug Administration in the treatment of actinic keratosis.^[6,18-20,23,28] Resiquimod which is an imidazole quinolone is 100 times more potent and acts similar to imiquimod activating Toll-like receptors 7 and 8. It is mainly used in the treatment of actinic keratosis and genital herpes simplex virus-II infection^[71,72] [Table 3].

TOPICAL AGENTS WITH TOLL-LIKE RECEPTOR ACTIVITY

Nicotinamide

Nicotinamide is a derivative of Vitamin B3, acts by retarding cytokine production and leucocyte chemotaxis. It is indicated in conditions such as bullous pemphigoid, necrobiosis lipoidica, dermatitis herpetiformis and acne, used both topically and systemically.^[73] Nicotinamide acts by downregulating interleukin-8 gene expression and interleukin-8 protein production by phosphorylation of mitogen-activated protein kinase and Toll-like receptor 2 dependent inhibitory kappa B degradation preventing the activation of nuclear factor kappa B.^[74]

Calcineurin inhibitors

Calcineurin inhibitors are potent immune suppressors which inhibits synthesis of proinflammatory cytokines in the T-cells (Toll-like receptor 2/6) by avoiding nuclear translocation of nuclear factor of activated T-cell.^[75]

ALL-TRANS RETINOIC ACID

All-trans retinoic acid is a Vitamin A derivative with anti-inflammatory properties. In a study by Liu *et al.*^[76] the effect of all-trans retinoic acid on Toll-like receptor expression showed a decreased Toll-like receptor 2 and CD14 expression by 41% and 42%, respectively. The mode of action of all-trans retinoic acid in acne is by the hampered *P. acnes* dependent activation of Toll-like receptor 2 and Toll-like receptor 4.

Adapalene

Adapalene acts by binding selectively to gamma and beta subtype of retinoic acid receptors in the epidermis and dermis. It acts by reducing the expression of Toll-like receptor 2 on keratinocytes in acne, thus limiting the inflammatory reaction around the pilosebaceous follicle.^[77]

Zinc

Zinc acts as an immunomodulator by hindering neutrophilic chemotaxis, the growth of *P. acnes*, activation of NK cells and activation of phagocytosis by granulocytes in acne.^[75,78-80] In a study by Jarrousse *et al.*^[81] the anti-inflammatory mechanism of zinc is through modulation of Toll-like receptor 2 surface expression. Zinc salts significantly decrease Toll-like receptor 2 expression in a dose dependent manner.

Sodium tosylchloramide

It is a disinfectant and acts by suppressing the activity of bacteria, virus, yeast and fungi. Anti-inflammatory properties of this compound are mediated by altering Toll-like receptor 4 related pathways which include the direct interaction of Toll-like receptor 4 with nicotinamide adenine dinucleotide phosphate oxidase, nuclear factor kappa B and dendritic cell activation.

NEWER TOPICAL AGENTS FOR SKIN CONDITIONS

CpG-ODN

It is a synthetic oligodeoxy nucleotide acts as LR-9 agonists and is considered to be safe adjuvants for vaccines and cancer immunotherapy due to better cell mediated as well as a humoral immune response.

CBT-SL5

P. acnes induces inflammation through the interaction of pathogen associated molecular patterns with Toll-like receptor 2 and Toll-like receptor 4 leading to the activation of nuclear factor kappa B. Antimicrobial peptides CBT-SL5, produced by *Enterococcus faecalis* has broad spectrum antimicrobial activity by repressing *P. acnes* induced translocation of nuclear factor kappa B into the nucleus, preventing activation of interleukin-8 gene expression and protein synthesis. The effects of CBT-SL5 on *P. acnes* induced inflammation was studied by Lee *et al.*^[82]

Table 1: TLRs and their ligands Tables

Table 1. Toll-like receptors and their ligands	
Toll-like Receptors	Ligands
TLR 2	Peptidoglycan (PGN), Lipopolysaccharides (LPS), Lipoteichoic acid (LTA), Lipoproteins, arabinoside-terminated lipoarabinomannan (AraLAM).
TLR 3	ds-RNA
TLR 4	Gram-negative Lipopolysaccharides, Taxol, Heat Shock Protein(HSP) 60/ 70/ 90, β -defensin, Fibronectin, Heparan sulfate
TLR 5	Flagellin
TLR 1/6	Heterodimerize with TLR2
TLR 7/8	ss-RNA, Imidazoquinoline
TLR 9	Bacterial DNA(CpG)
TLR 10/11	Not Known

TLR: Toll-like receptor.

Table 2: Toll-like receptors in dermatology.

Table 2: Toll-like Receptors in Dermatology		
Toll-like receptor	Disease	Function with the disease
TLR 1, 2	Leprosy	TLR function and signalling lead to disease progression
TLR 1–4, 5, 9	Psoriasis	TLRs upregulation and helps in the creation of autoreactive T cells
TLR 1/2 (heterodimers), 4, 6	Borreliosis/Lyme disease	TLR upregulation with eventual exacerbation of the disease
TLR 2,3, 4	Vaccinia	TLRs help in viral clearance but are targeted by viral products which suppress host defense
TLR 2, 3, 9	Herpes simplex/Varicella zoster	TLR 2 polymorphism associated with disease severity, TLR 3 and 9 help in viral clearance
TLR 2, 4	Sarcoidosis	TLR polymorphism associated with disease severity
TLR 2, 4/5 (heterodimer)	Syphilis	TLR activate the immune system
TLR 2, 4, CD14	Acne vulgaris	TLR upregulation with eventual exacerbation of the disease
TLR 2, 4-CD14	Yersinia spp—the plague	Pathogen exploits TLR pathway to survive
TLR 2, 4-CD14, 6	Candida albicans	TLR function and signalling leads to disease progression
TLR 2, 6	Staph. Aureus	TLR 2 polymorphism associated with severity, TLR 2/6 function and signalling lead to disease progression
TLR 2, 9	Atopic dermatitis	TLR polymorphism leading to increased susceptibility
TLR 3	Stevens-Johnson syndrome/Toxic epidermal necrolysis	TLR polymorphism linked to disease severity
TLR 3, 7, 9	Lupus erythematosus	TLR 7 upregulation and TLR 3, TLR 9 helps to create autoreactive cells
TLR 3,7,9	Verruca and Molluscum Contagiosum	TLR 3, 9 help in immune activation, TLR 7 possible association with disease exacerbation, proposed target for therapy
TLR 4	Cutaneous graft versus host disease	Exacerbation disease in response to LPS
TLR 4	Scleroderma	TLR function and signalling lead to disease progression
TLR 4, 6	Behcet's disease-vasculitis	TLR 4 polymorphism leads to increased susceptibility, differential regulation of TLR 6 helps in progression of disease
TLR 4, 7, 9	Melanoma	TLR 4 exacerbates disease TLR 7,9-targeted for immune modulation
TLR 7, 8	Squamous cell carcinoma	Exacerbation of disease, being studied to target for therapy
TLR 7, 8, 9	Basal cell carcinoma	Exacerbation of disease, target for therapy
TLR 9	Lichen planus	TLR upregulation with eventual exacerbation of the disease

Table 3: Current and potential systemic agents targeting Toll-like receptors for the treatment of several dermatological conditions

TABLE 3. Current and potential systemic agents targeting TLRs for the treatment of several dermatological conditions			
Toll-like Receptor	Name of Systemic Agent	Agonist(Ag) or Antagonist (Ant)	Indication or Potential Indication
TLR 3	Ampligen	Ag	Cancer
TLR 4	Taxol	Ag	Cancers such as melanoma
TLR 4	MPL	Ag	Papillomavirus, genital herpes
TLR 7	Sotirmod, R-850	Ag	Actinic keratoses
TLR 7	851	Ag	cHPV
TLR 7	852A	Ag	Melanoma, various leukemias
TLR 9	CpG7909 (CpG2006, PF-3512676 or ProMune) B-type	Ag	Non-small cell lung cancer (with chemo), melanoma, CTCL, NHL, BCC, RCC, breast cancer, CLL
TLR 9	VaxImmune (CpG7909) B-type	Ag	Infectious diseases and cancers, breast cancer, melanoma
TLR 9	IRS 954	Ant	Lupus
MPL: 3-de-O-acylated monophosphoryl lipid A HPV: Human papillomavirus CTCL: Cutaneous T cell lymphoma NHL: Nonhodgkin's lymphoma BCC: Basal cell carcinoma RCC: Renal cell carcinoma CLL: Chronic lymphocytic leukemia			

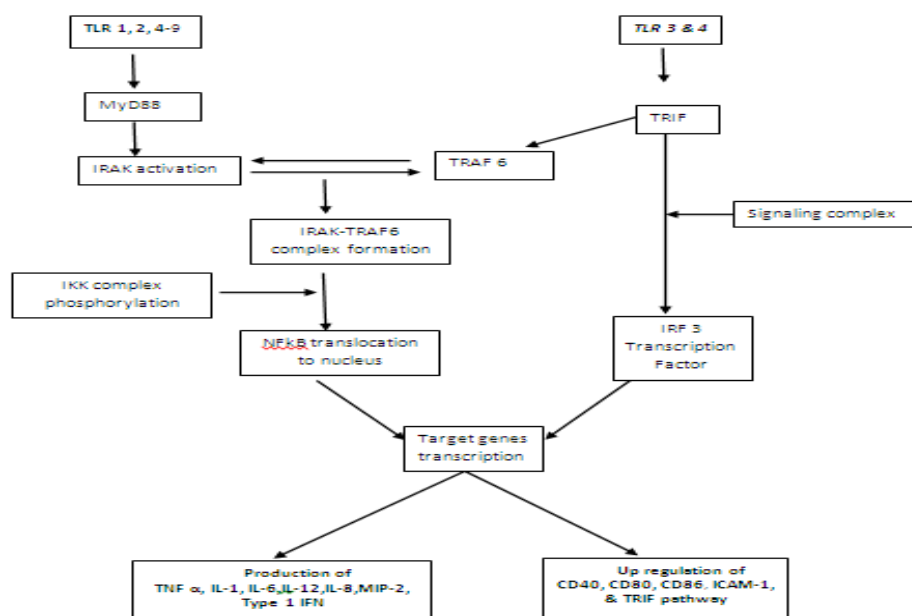


Figure -1

CONCLUSION

Toll-like receptors are a group of receptors that play a major role in innate and adaptive immunity. There has been a significant advance in the understanding of Toll-like receptors in skin infections, inflammatory conditions like psoriasis, L.P, acne cutaneous malignancies and their role in therapeutics. These receptors are activated by various ligands present in pathogenic organisms and have different adaptors which respond to activation and are located at the cell surface or internal cell compartments.

A number of skin diseases are associated with Toll-like receptors. Toll-like receptor agonists and antagonists offer a great therapeutic potential in the treatment of skin diseases and further studies are required to know the efficacy of vaccines on Toll-like receptors and their long-term effects.

Source of Support

Nil.

Conflicts of Interest

None declared.

REFERENCES

- Hansson GK, Edfeldt K. Toll to be paid at the gateway to the vessel wall. *Arterioscler Thromb Vasc Biol*, 2005; 25: 1085-7.
- Available from: <http://www.aerzteblatt.de/archive/55316>.
- Takeda K, Akira S. TLR signaling pathways. *Semin Immunol*, 2004; 16: 3-9.
- Takeda K, Kaisho T, Akira S. Toll-like receptors. *Annu Rev Immunol*, 2003; 21: 335-76.
- Iwasaki A, Medzhitov R. Toll-like receptor control of the adaptive immune responses. *Nat Immunol*, 2004; 5: 987-95.
- Miller LS. Toll-like receptors in skin. *Adv Dermatol*, 2008; 24: 71-87.
- Netea MG, van der Graaf C, Van der Meer JW, Kullberg BJ. Toll-like receptors and the host defense against microbial pathogens: Bringing specificity to the innate-immune system. *J Leukoc Biol*, 2004; 75: 749-55.
- Renn CN, Sanchez DJ, Ochoa MT, Legaspi AJ, Oh CK, Liu PT, et al. TLR activation of Langerhans cell-like dendritic cells triggers an antiviral immune response. *J Immunol*. 2006; 177: 298-305.
- Yu N, Zhang S, Zuo F, Kang K, Guan M, Xiang L. Cultured human melanocytes express functional toll-like receptors 2-4, 7 and 9. *J Dermatol Sci.*, 2009; 56: 113-20.
- Mempel M, Kalali BN, Ollert M, Ring J. Toll-like receptors in dermatology. *Dermatol Clin*, 2007; 25: 531-40, viii.
- Medzhitov R. Toll-like receptors and innate immunity. *Nat Rev Immunol*, 2001; 1: 135-45.
- Shimazu R, Akashi S, Ogata H, Nagai Y, Fukudome K, Miyake K, et al. MD-2, a molecule that confers lipopolysaccharide responsiveness on Toll-like receptor 4. *J Exp Med*, 1999; 189: 1777-82.
- Wright SD, Tobias PS, Ulevitch RJ, Ramos RA. Lipopolysaccharide (LPS) binding protein opsonizes LPS-bearing particles for recognition by a novel receptor on macrophages. *J Exp Med*, 1989; 170: 1231-41.
- Dorothea Terhorst, Behman Naderi katali, Markus Ollert, Johannes Ring and Martin Mempel. Role of toll like receptors in Host Defenses and their relevance to Dermatologic Diseases. *Am J Clin Dermatol*, 2010; 11(oct-10).
- Mempel M, Voelcker V, Köllisch G, Plank C, Rad R, Gerhard M, et al. Toll-like receptor expression in human keratinocytes: Nuclear factor kappaB controlled gene activation by *Staphylococcus aureus*

- is toll-like receptor 2 but not toll-like receptor 4 or platelet activating factor receptor dependent. *J Invest Dermatol*, 2003; 121: 1389-96.
16. Lee Y, Kim H, Kim S, Kim KH, Chung JH. Activation of toll-like receptors 2, 3 or 5 induces matrix metalloproteinase-1 and -9 expression with the involvement of MAPKs and NF-kappaB in human epidermal keratinocytes. *Exp Dermatol*, 2010; 19: e44-9.
 17. Lai Y, Gallo RL. Toll-like receptors in skin infections and inflammatory diseases. *Infect Disord Drug Targets*, 2008; 8: 144-55.
 18. Kang SS, Kauls LS, Gaspari AA. Toll-like receptors applications to dermatologic disease. *J Am Acad Dermatol*, 2006; 5: 951-83.
 19. Sandor F, Buc M. Toll-like receptors. I. Structure, function and their ligands. *Folia Biol (Praha)*, 2005; 51: 148-57.
 20. Schnare M, Barton GM, Holt AC, Takeda K, Akira S, Medzhitov R. Toll-like receptors control activation of adaptive immune responses. *Nat Immunol*, 2001; 2: 947-50.
 21. Lebre MC, Antons JC, Kalinski P, Schuitemaker JH, van Capel TM, Kapsenberg ML, *et al.* Double-stranded RNA-exposed human keratinocytes promote Th1 responses by inducing a type-1 polarized phenotype in dendritic cells: Role of keratinocyte-derived tumor necrosis factor alpha, type I interferons, and interleukin-18. *J Invest Dermatol*, 2003; 120: 990-7.
 22. Tomai MA, Miller RL, Lipson KE. Immune response modifiers: Imiquimod and future drugs for modulating the immune response. *Drug Discov Today Strateg*, 2006; 3: 343-52.
 23. Tse K, Horner AA. Update on toll-like receptor-directed therapies for human disease. *Ann Rheum Dis*, 2007; 66 Suppl 3: iii 77-80.
 24. Kawai T, Akira S. Signaling to NF-kappaB by toll-like receptors. *Trends Mol Med*, 2007; 13: 460-9.
 25. Alvarez JI. Inhibition of toll like receptor immune responses by microbial pathogens. *Front Biosci*, 2005; 10: 582-7.
 26. Valins W, Amini S, Berman B. The expression of toll-like receptors in dermatological diseases and the therapeutic effect of current and newer topical toll-like receptor modulators. *J Clin Aesthet Dermatol*, 2010; 3: 20-9.
 27. McInturff JE, Modlin RL, Kim J. The role of toll-like receptors in the pathogenesis and treatment of dermatological disease. *J Invest Dermatol*, 2005; 125: 1-8.
 28. McGirt LY, Beck LA. Innate immune defects in atopic dermatitis. *J Allergy Clin Immunol*, 2006; 118: 202-8.
 29. Cho SH, Strickland I, Boguniewicz M, Leung DY. Fibronectin and fibrinogen contribute to the enhanced binding of *Staphylococcus aureus* to atopic skin. *J Allergy Clin Immunol*, 2001; 108: 269-74.
 30. Nishijima S, Namura S, Kawai S, Hosokawa H, Asada Y. *Staphylococcus aureus* on hand surface and nasal carriage in patients with atopic dermatitis. *J Am Acad Dermatol*, 1995; 32: 677-9.
 31. Hasannejad H, Takahashi R, Kimishima M, Hayakawa K, Shiohara T. Selective impairment of toll-like receptor 2-mediated proinflammatory cytokine production by monocytes from patients with atopic dermatitis. *J Allergy Clin Immunol*, 2007; 120: 69-75.
 32. Oh DY, Schumann RR, Hamann L, Neumann K, Worm M, Heine G. Association of the toll-like receptor 2 A-16934T promoter polymorphism with severe atopic dermatitis. *Allergy*, 2009; 64: 1608-15.
 33. Petry V, Gaspari AA. Toll-like receptors and dermatology. *Int J Dermatol*, 2009; 48: 558-70.
 34. Ahmad-Nejad P, Mrabet-Dahbi S, Breuer K, Klotz M, Werfel T, Herz U, *et al.* The toll-like receptor 2 R753Q polymorphism defines a subgroup of patients with atopic dermatitis having severe phenotype. *J Allergy Clin Immunol*, 2004; 113: 565-7.
 35. Novak N, Yu CF, Bussmann C, Maintz L, Peng WM, Hart J, *et al.* Putative association of a TLR9 promoter polymorphism with atopic eczema. *Allergy*, 2007; 62: 766-72.
 36. Jin H, Kumar L, Mathias C, Zurakowski D, Oettgen H, Gorelik L, *et al.* Toll-like receptor 2 is important for the T(H)1 response to cutaneous sensitization. *J Allergy Clin Immunol*, 2009; 123: 875-82.e1.
 37. De Benedetto A, Agnihotri R, McGirt LY, Bankova LG, Beck LA. Atopic dermatitis: A disease caused by innate immune defects? *J Invest Dermatol*, 2009; 129: 14-30.
 38. Novak N. New insights into the mechanism and management of allergic diseases: Atopic dermatitis. *Allergy*, 2009; 64: 265-75.
 39. Ong PY, Ohtake T, Brandt C, Strickland I, Boguniewicz M, Ganz T, *et al.* Endogenous antimicrobial peptides and skin infections in atopic dermatitis. *N Engl J Med*, 2002; 347: 1151-60.
 40. Howell MD, Kim BE, Gao P, Grant AV, Boguniewicz M, DeBenedetto A, *et al.* Cytokine modulation of atopic dermatitis filaggrin skin expression. *J Allergy Clin Immunol*, 2007; 120: 1505.
 41. Akdis CA, Akdis M, Bieber T, Bindslev-Jensen C, Boguniewicz M, Eigenmann P, *et al.* Diagnosis and treatment of atopic dermatitis in children and adults: European Academy of Allergology and Clinical Immunology/American Academy of Allergy, Asthma and Immunology/PRACTALL Consensus Report. *J Allergy Clin Immunol*, 2006; 118: 152-69.
 42. Ruzicka T, Bieber T, Schöpf E, Rubins A, Dobozy A, Bos JD, *et al.* A short-term trial of tacrolimus ointment for atopic dermatitis. European Tacrolimus Multicenter Atopic Dermatitis Study Group. *N Engl J Med*, 1997; 337: 816-21.
 43. Büchau AS, Schaubert J, Hultsch T, Stuetz A, Gallo RL. Pimecrolimus enhances TLR2/6-induced

- expression of antimicrobial peptides in keratinocytes. *J Invest Dermatol*, 2008; 128: 2646.
44. Applegate LA, Ley RD, Alcalay J, Kripke ML. Identification of the molecular target for the suppression of contact hypersensitivity by ultraviolet radiation. *J Exp Med*, 1989; 170: 1117-31.
 45. Morison WL. Photoimmunology. *J Invest Dermatol*, 1981; 77: 71-6.
 46. Scheinfeld NS, Tutrone WD, Weinberg JM, DeLeo VA. Phototherapy of atopic dermatitis. *Clin Dermatol*, 2003; 21: 241-8.
 47. Kang SS, Kauls LS, Gaspari AA. Toll-like receptors: Applications to dermatologic disease. *J Am Acad Dermatol*, 2006; 54: 951-83.
 48. Hari A, Flach TL, Shi Y, Mydlarski PR. Toll-like receptors: Role in dermatologic disease. *Mediators Inflamm*, 2010; 2010: 437246.
 49. Schmidt M, Raghavan B, Müller V, Vogl T, Fejer G, Tchaptchet S, *et al.* Crucial role for human toll-like receptor 4 in the development of contact allergy to nickel. *Nat Immunol*, 2010; 11: 814-9.
 50. Gilliet M, Conrad C, Geiges M, Cozzio A, Thürlimann W, Burg G, *et al.* Psoriasis triggered by toll-like receptor 7 agonist imiquimod in the presence of dermal plasmacytoid dendritic cell precursors. *Arch Dermatol*, 2004; 140: 1490-5.
 51. Wu JK, Siller G, Strutton G. Psoriasis induced by topical imiquimod. *Australas J Dermatol*, 2004; 45: 47-50.
 52. Litjens NH, Rademaker M, Ravensbergen B, Rea D, van der Plas MJ, Thio B, *et al.* Monomethylfumarate affects polarization of monocyte-derived dendritic cells resulting in down-regulated Th1 lymphocyte responses. *Eur J Immunol*, 2004; 34: 565-75.
 53. Schön MP. Animal models of psoriasis – What can we learn from them? *J Invest Dermatol*, 1999; 112: 405-10.
 54. O'Neill LA. Therapeutic targeting of toll-like receptors for inflammatory and infectious diseases. *Curr Opin Pharmacol*, 2003; 3: 396-403.
 55. Cristiane Beatriz de OLIVEIRA, Cidia VASCONCELLOS, Neusa Y. SAKAI-VALENTE *et al.* Toll like receptors 2 and 4 expression of keratinocytes from patients with localized and disseminated dermatophytosis. *Rev. Inst. Med. Trop. Sao Paulo*, 2015; 57(1): 57-61.
 56. Krutzik SR, Ochoa MT, Sieling PA, Uematsu S, Ng YW, Legaspi A, *et al.* Activation and regulation of toll-like receptors 2 and 1 in human leprosy. *Nat Med*, 2003; 9: 525-32.
 57. Zaba LC, Krueger JG, Lowes MA. Resident and "inflammatory" dendritic cells in human skin. *J Invest Dermatol*, 2009; 129: 302-8.
 58. Hofmann MA, Kors C, Audring H, Walden P, Sterry W, Trefzer U. Phase 1 evaluation of intralesionally injected TLR9-agonist PF-3512676 in patients with basal cell carcinoma or metastatic melanoma. *J Immunother*, 2008; 31: 520-7.
 59. Voelcker V, Gebhardt C, Averbek M, Saalbach A, Wolf V, Weih F, *et al.* Hyaluronan fragments induce cytokine and metalloprotease upregulation in human melanoma cells in part by signalling via TLR4. *Exp Dermatol*, 2008; 17: 100-7.
 60. Miller LS, Modlin RL. Toll-like receptors in the skin. *Semin Immunopathol*, 2007; 29: 15-26.
 61. Liu L, Zhou X, Shi J, Xie X, Yuan Z. Toll-like receptor-9 induced by physical trauma mediates release of cytokines following exposure to CpG motif in mouse skin. *Immunology*, 2003; 110: 341-7.
 62. Wang J, Hori K, Ding J, Huang Y, Kwan P, Ladak A, *et al.* Toll-like receptors expressed by dermal fibroblasts contribute to hypertrophic scarring. *J Cell Physiol*, 2011; 226: 1265-73.
 63. Schaubert J, Dorschner RA, Coda AB, Büchau AS, Liu PT, Kiken D, *et al.* Injury enhances TLR2 function and antimicrobial peptide expression through a Vitamin D-dependent mechanism. *J Clin Invest*, 2007; 117: 803-11.
 64. Gregorio J, Meller S, Conrad C, Di Nardo A, Homey B, Lauerma A, *et al.* Plasmacytoid dendritic cells sense skin injury and promote wound healing through type I interferons. *J Exp Med*, 2010; 207: 2921-30.
 65. Marshak-Rothstein A. Toll-like receptors in systemic autoimmune disease. *Nat Rev Immunol*, 2006; 6: 823-35.
 66. Krieg AM. Therapeutic potential of toll-like receptor 9 activation. *Nat Rev Drug Discov*, 2006; 5: 471-84.
 67. Christensen SR, Shupe J, Nickerson K, Kashgarian M, Flavell RA, Shlomchik MJ. Toll-like receptor 7 and TLR9 dictate autoantibody specificity and have opposing inflammatory and regulatory roles in a murine model of lupus. *Immunity*, 2006; 25: 417-28.
 68. Berman B, Amini S, Valins W, Block S. Pharmacotherapy of actinic keratosis. *Expert Opin Pharmacother*, 2009; 10: 3015-31.
 69. Berman B, Viera M, Amini S, Valins W. Immune response modulators in the treatment of skin cancer. In: Rigel, *et al.*, editor. *Cancer of Skin*. 2nd ed., Ch. 44. Philadelphia, PA: Elsevier, Inc.; ??? [In press].
 70. Fife KH, Meng TC, Ferris DG, Liu P. Effect of resiquimod 0.01% gel on lesion healing and viral shedding when applied to genital herpes lesions. *Antimicrob Agents Chemother*, 2008; 52: 477-82.
 71. Mark KE, Corey L, Meng TC, Magaret AS, Huang ML, Selke S, *et al.* Topical resiquimod 0.01% gel decreases herpes simplex virus type 2 genital shedding: A randomized, controlled trial. *J Infect Dis.*, 2007; 195: 1324-31.
 72. Shalita AR, Smith JG, Parish LC, Sofman MS, Chalker DK. Topical nicotinamide compared with clindamycin gel in the treatment of inflammatory acne vulgaris. *Int J Dermatol*, 1995; 34: 434-7.
 73. Grange PA, Raingeaud J, Calvez V, Dupin N. Nicotinamide inhibits *Propionibacterium acnes*-induced IL-8 production in keratinocytes through the NF-kappaB and MAPK pathways. *J Dermatol Sci.*, 2009; 56: 106-12.

74. Dreno B, Foulc P, Reynaud A, Moyse D, Habert H, Richet H. Effect of zinc gluconate on *Propionibacterium acnes* resistance to erythromycin in patients with inflammatory acne: *In vitro* and *in vivo* study. *Eur J Dermatol*, 2005; 15: 152-5.
75. Liu PT, Krutzik SR, Kim J, Modlin RL. Cutting edge: All-trans retinoic acid down-regulates TLR2 expression and function. *J Immunol*, 2005; 174: 2467-70.
76. Tenaud I, Khammari A, Dreno B. *In vitro* modulation of TLR-2, CD1d and IL-10 by adapalene on normal human skin and acne inflammatory lesions. *Exp Dermatol*, 2007; 16: 500-6.
77. Dreno B, Trossaert M, Boiteau HL, Litoux P. Zinc salts effects on granulocyte zinc concentration and chemotaxis in acne patients. *Acta Derm Venereol*, 1992; 72: 250-2.
78. Strauss JS, Stranieri AM. Acne treatment with topical erythromycin and zinc: Effect of *Propionibacterium acnes* and free fatty acid composition. *J Am Acad Dermatol*, 1984; 11: 86-9.
79. Chvapil M, Stankova L, Zukoski C 4th, Zukoski C 3rd. Inhibition of some functions of polymorphonuclear leukocytes by *in vitro* zinc. *J Lab Clin Med*, 1977; 89: 135-46.
80. Jarrousse V, Castex-Rizzi N, Khammari A, Charveron M, Dréno B. Zinc salts inhibit *in vitro* toll-like receptor 2 surface expression by keratinocytes. *Eur J Dermatol*, 2007; 17: 492-6.
81. Lee YJ, Choi HJ, Kang TW, Kim HO, Chung MJ, Park YM. CBT-SL5, a bacteriocin from *Enterococcus faecalis*, suppresses the expression of interleukin-8 induced by *Propionibacterium acnes* in cultured human keratinocytes. *J Microbiol Biotechnol*, 2008; 18: 1308-16.