Expression Of Soluble Toll- Like Receptors And Its Correlation With The Oxidative Damage In Diseased Conditions

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Expression Of Soluble Toll- Like Receptors And Its Correlation With The Oxidative Damage In Diseased Conditions

Author(s): Karki K, Negi R, Pande D, Khanna R S, Khanna H D

Overview

Infections caused by different pathogens are often associated with systemic symptoms and may compromise the functional integrity. In the mediation of the systemic effect of pathogens Toll-like receptors (TLRs) play a significant role. TLRs are a type of pattern recognition receptor and recognize molecules that are broadly shared by pathogens but distinguishable from host molecules. TLRs are broadly distributed on cells of the immune system and function as primary sensors of invading pathogens. There is also growing experimental evidence indicating that Toll-like receptors are expressed on different non-immune cell types as well, like epithelial or endothelial cells.

Oxidative stress significantly up-regulate the expression of these receptors whereas TNF-alpha up-regulates the expression of TLR2 and TLR3. Furthermore the activation of TLR2/6 leads to an increased permeability which is accompanied by a down regulation of occludin and claudin-5 expression and disappearance of these tight junction proteins from the cell membrane.

Cell biology of TLRs provides new opportunities for drug development for drug intervention to manipulate immune responses. TLRs are mostly associated with initiation of the innate response and inflammation, and inhibition of TLR activity- which may help combat an over active innate response characteristic of numerous inflammatory disorders.

Introduction

The role of TLRs in the adaptive immune response needs to be studied. A diverse range of microbes, including viruses, bacteria, and fungi stand ready to attack the human body and thrive in the nutrient rich environment it provides. Fortunately, the immune response functions as a defense mechanism and counter attacks by recognizing and destroying foreign invaders. But what alerts the body to danger? How are the foreign organisms detected? The discovery of microbial sensing proteins called Toll- like receptors is helping to answer these questions in understanding of the response to infection such as AIDS, Hepatitis, Malaria, and even Cancer1.

Toll Like Receptors

Toll receptor was originally identified in Drosophila as an essential receptor for the establishment of the dorso-ventral pattern in developing embryos2. In 1996, Hoffmann and colleagues demonstrated that Toll-mutant flies were highly susceptible to fungal infection3. This study points that the immune system, particularly the innate immune system, has a skillful means of detecting invasion by microorganisms. Subsequently, mammalian homologues of Toll receptor were identified one after another, and designated as Toll-like receptors (TLRs). Functional analysis of mammalian TLRs has revealed that they recognize specific patterns of microbial components that are conserved among pathogens, but are not found in mammals. In signaling pathways via TLRs, a common adaptor, MyD88, was first characterized as an essential component for the activation of innate immunity by all the TLRs. However, accumulating evidence indicates that individual TLRs exhibit specific responses. Furthermore, they have their own signaling molecules to manifest these specific responses.

TLRs are type I transmembrane glycoproteins which are structurally characterized by extracellular leucine rich repeats (LPRs) and Toll/IL-1 receptor (TIR) signaling domains. The first TLR to be characterized was TLR4 and the family has now been expanded to include 10 members in humans4,5. The immune system consists of two closely related systems known as the innate and adaptive immune systems. The adaptive immune system responds to specific 'non-self' antigens and generates immunological memory. In contrast, the innate immune system provides an immediate first line of defense against a diverse repertoire of invading microbial pathogens. The key components of innate immunity, cognate pattern recognition receptors (PRRs), are considered to act as sentinels against both invading organisms bearing pathogen-associated molecular patterns (PAMPs) and damage-associated molecular pattern molecules (DAMPs). Toll-like receptors (TLRs) are good examples of these receptors6. Because of their wide-ranging impact upon both innate and adaptive
immunity in several disease settings, TLRs and their signaling pathways emerge as attractive therapeutic targets. This summarizes the main players in innate immune signaling and highlights possible drug targets in various disease settings. Innate immune responses are triggered mainly by a spectrum of ‘danger’ signals referred to as PAMPs and DAMPs. PAMPs are exogenous molecules derived from both pathogenic and non-pathogenic microbes. In contrast, the vast majority of DAMPs are endogenous molecules released from dying host cells molecules upon cellular stress or tissue damage4,5,7,8. The TLRs are a family of evolutionarily conserved PRRS that play a key role in sensing the microbial world. Different TLR members are reported to recognize and respond to different PAMPs and some endogenous DAMPs9, thus initiating innate immune responses and priming antigen-specific adaptive immunity, both in infectious and non-infectious disease scenarios.

**TLR signaling and disease**

TLRs constitute a primary defense mechanism in both infections and some non-infectious disease settings in mammals. Activation of TLRs and the MyD88 signaling pathway plays a protective role during infection with several pathogens, including protozoan parasites and pyogenic bacteria10. Patients with autosomal recessive MyD88 deficiency have been reported to suffer from life-threatening, often recurrent pyogenic bacterial infections. Interestingly, however, their clinical status improved in later life, alluding to the compensatory effect of adaptive immunity. Consistent with their vital role in fighting infections, down regulation of TLR-related molecules or signaling has been associated with sepsis and autoimmune disease. On the other hand, up-regulation of these molecules has been linked to cancer, allergy, other autoimmune diseases and immune abnormalities in HIV11,12.

**A) Role of TLRs in HIV infection**

HIV infection is characterized by progressive immune dysfunction, leading to AIDS and opportunistic infections by a wide variety of microorganisms. Infections with pathogenic and non-pathogenic organisms activate the cellular transcription factor, NF-κB, which then binds to consensus binding sites in the HIV-LTR to initiate HIV transcription. Toll-like receptors (TLRs) are innate immune system receptors expressed on cells of the innate immune system that mediate NF-κB activation by a variety of bacterial, mycobacterial, spirochetal, and viral pathogen-associated molecular patterns (PAMP). HIV-infected patients are frequently co-infected with multiple organisms that can induce HIV replication synergistically or additively. In in- vitro and in vivo systems, co-stimulation with multiple PAMP is known to induce NF-κB activation and inflammatory cytokine production synergistically 13,14.

Chronic or recurrent infections contribute to sustained high levels of viremia and thereby accelerate HIV disease progression and immune deterioration. Whalen et al. demonstrated that active M. tuberculosis infection is associated with decreased survival among HIV-1-infected individuals after controlling for CD4_ cell count, antiretroviral therapy, and previous opportunistic infections. Alcabes et al. reported an accelerated rate of CD4_ cell decline in HIV-infected individuals during bacterial infections. The development of an opportunistic infection was shown to be an independent risk factor for death in HIV-infected population 15. The innate immune activation driven HIV replication may in part explain the aggressive course of HIV infection in individuals co-infected with M. Tuberculosis and may provide a possible mechanism for the more rapid course of immunologic decline among HIV-infected patients in sub-Saharan Africa, where coinfections are common and often continuous. Currently the molecular mechanisms involved in enhanced HIV replication and the progression of HIV infection following multiple opportunistic infections, such as mycobacterial infections, are not well understood. Therefore, delineating the molecular mechanisms that regulate activation of latent HIV during infections with opportunistic and pathogenic microorganisms is of great clinical significance.

**B) Role of TLRs in Breast Cacinoma**

Breast cancer is one of the common occurring in women which is incurable and ultimately claims the life of the patient with complications. Thus, there is a need for new and effective breast cancer therapies. Significant progress has been made in the development of new therapies for the treatment of breast cancer. Nonetheless, approximately 40% of women with breast cancer fail primary treatments. As TLRs are widely expressed on tumor cells and play important roles in the initiation and progression of cancer, they may thus serve an important target and have an effective perspective on breast cancer treatment. TLR recognize and respond to exogenous and endogenous ligands through signaling pathways leading to inflammatory cascade mediator production which direct the innate and adaptive immune response. It is increasingly recognized that inflammatory processes play a key role in tumorigenesis16.

**C) Toll- Like Receptor Links Immunity, Oxidation And Angiogenesis**
Inflammation is known to cause oxidative stress and the growth of new blood vessels, and now a molecular mechanism linking these processes has been found. Oxidized products of lipid oxidation—(carboxy alkyl) pyrrole protein adducts—are generated during inflammation and wound healing. These products are shown to act as endogenous agonists for Toll-like receptor 2 (TLR2), which stimulates blood vessel growth through a mechanism that is independent of vascular endothelial growth factor 17. Reactive oxygen species (ROS) such as hydrogen peroxide (H2O2) and superoxide anion are generated in inflamed tissues and are reported to contribute to the pathogenesis of inflammatory lung diseases including chronic obstructive pulmonary diseases (COPD) 18, bronchial asthma 19, cystic fibrosis 20, and idiopathic pulmonary fibrosis 21. Large amounts of ROS derived from inflammatory cells cause pro-inflammatory cytokine production. Among inflammatory cells, neutrophils are a key player in the inflammatory lung diseases. It is well-known that excessive infiltration of neutrophils is observed in the airways during exacerbations induced by viral infections 22.

Toll-like receptors (TLRs) are simple pattern recognition receptor systems and are known to react with conserved molecular patterns of pathogens 23. The innate immunity cells also act against viral infections through TLRs including TLR3, TLR7 and TLR8. Human neutrophils possess all functional TLRs except TLR3, and their agonists enhance neutrophil functions such as cytokine release, superoxide generation and phagocytosis 24. TLR7 and TLR8, located in the endosome, act as anti-viral receptors for recognizing single strand RNA (ssRNA), which is present at various phases of viral infection from viral entry to replication. After TLR7 and TLR8 are activated by ssRNA, their signals are transduced through myeloid differentiation primary response gene 88 (MyD-88) and tumor necrosis factor (TNF) receptor-associated factor 6 (TRAF6) leading to enhanced nuclear factor-kappa B (NF-kB) DNA binding activity 25. Activation of NF-kB leads to increased inflammatory gene products such as interleukin-8 (IL-8) and GM-CSF causing neutrophilic inflammation during viral infection. Resiquimod (R848), a potent synthetic agonist of TLR 7/8 has been reported to simulate the effects of ssRNA viruses on TLR 7/8, to prime human neutrophils 26, and then increase the biosynthesis of lipid mediators through NF-kB activation suggesting that TLR7 and TLR8 activation might affect the neutrophilic responses.

References

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Reviews

Review 1

Review Title: Expression of soluble Toll like receptors and its correlation with the oxidative stress in diseased conditions

Posted by Prof. Deepak Bhatnagar on 04 May 2011 05:41:28 PM GMT

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Rating: 7

Comment:
The authors have shown the role of TLR’s in health and diseases. The down regulation of TLR related molecules or signaling as well as their up regulation has been shown in some of the disorders. The TLR mutants may be more prone to certain infections. The role of TLR is of importance in evolving therapeutic drug approach in various diseases. The oxidative stress in various diseases may be one of the factors in TLR regulation. Oxidative stress has been observed in various diseases due to formation of oxidized products, often exhibited as lipid peroxidation and changes in the antioxidant system. The paper is well written and includes good information on TLR.

Competing interests: No

Invited by the author to make a review on this article? : Yes

Experience and credentials in the specific area of science:
The major area of our research is on free radical generation and role of antioxidants in various diseases. There are various conditions of toxicity including heavy metal and pesticide intoxication, where free radicals are formed. Some other area of our work includes antioxidants in foods such as polyphenols, isoflavones etc, which may have contribution in lowering oxidative stress.

Publications in the same or a related area of science: No

How to cite: Bhatnagar D.Expression of soluble Toll like receptors and its correlation with the oxidative stress in diseased conditions[Review of the article ‘Expression Of Soluble Toll- Like Receptors And Its Correlation With The Oxidative Damage In Diseased Conditions ‘ by ].WebmedCentral 1970;2(5):REVIEW_REF_NUM724
Review 2

**Review Title:** Expression of soluble toll like receptors and its correlation with the oxidative damage in diseased conditions.

Posted by Prof. D Dhawan on 14 Apr 2011 10:00:05 AM GMT

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**Rating:** 7

**Comment:**
The review article from H.D Khanna' s lab is well written and covers many aspects with regard to the role of toll like receptors in various diseases. The article may be accepted as such with the comment that words 'oxidative damage' can be deleted from the title as the paper is general in nature. Further some references in the text like Whalen et al etc should mention the year also.

**Competing interests:** No competing interests.

**Invited by the author to make a review on this article?** : No

**Experience and credentials in the specific area of science:**
we have worked extensively in the area of oxidative stress induced by heavy metals as well as in lung and colon cancers. However, we have not worked on toll like receptors.

**Publications in the same or a related area of science:** Yes

**References:**

**How to cite:**
Dhawan D.Expression of soluble toll like receptors and its correlation with the oxidative damage in diseased conditions.[Review of the article 'Expression Of Soluble Toll- Like Receptors And Its Correlation With The Oxidative Damage In Diseased Conditions ' by ].WebmedCentral 1970;2(4):REVIEW_REF_NUM675
Review 3

Review Title: Review for paper by Karki et al

Posted by Dr. Ravi Kiran on 25 Mar 2011 07:42:41 AM GMT

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Rating: 7

Comment:
The paper is well written and the findings are interesting. It is a significant advancement in the existing knowledge

Competing interests: No

Invited by the author to make a review on this article? : No

Experience and credentials in the specific area of science:
Yes

Publications in the same or a related area of science: Yes

How to cite: Kiran R.Review for paper by Karki et al[Review of the article ‘Expression Of Soluble Toll- Like Receptors And Its Correlation With The Oxidative Damage In Diseased Conditions ’ by ].WebmedCentral 1970;2(3):REVIEW_REF_NUM624
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