Review Article

University J Dent Scie 2025; Vol. 11, Issue 2

Toll-like Receptors : Structure, signaling, and Role in Oral Carcinogenesis and Various Diseases : A Narrative Review

Abstract:
Toll-like receptors or TLRs are members of the altered inheritance of PRRs (pattern recognition receptors). They impersonate an important province in linking innate immunity with adaptive immunity. The expression and location of TLRs are controlled as opposed to specialized molecules that elaborate from damaged host cells or pathogens. Over expression of Toll-like receptors can cause agitation of immune homeostasis and mark up the chance of autoimmune and inflammatory diseases. This review examines existing documents in the literature on toll-like receptors. Several databases, including Pubmed,Science Direct, Scopus, and Google Scholar, were searched for papers. Keywords used in the search are "Toll-like receptors", "TLR signaling", "TLR in disease", "TLR in mouth carcinogenesis".

Key-words:TLRs, Toll-like receptor, Oral carcinogenesis, Signaling,

Introduction:

Toll-like receptors, often known as TLRs, are a class of pattern recognition receptors (PRRs) that trigger innate immune responses by searching for conserved chemical patterns that indicate infections. Type I transmembrane proteins are the toll-like receptors composed of three structural domains. These domains are the leucine-rich repeat (LRR) motif domain, the Toll/IL-1 cytoplasmic receptor domain, and the transmembrane domain. LRR-motif domains are useful for understanding pathogens. The cytoplasmic Toll/IL-1 receptor domain initiates signaling by communicating with signaling adapters.[1,2]

Molecules widely distributed by pathogens. H. DAMPs and PAMPs can be distinguished by Toll-like receptors.[3,4] This type of identification is multifaceted. That is, it depends on the type of Toll-like receptor. For example, mouse TLR 13 helps identify bacterial 23S rRNA, and mammalian TLR4 helps identify LPS (lipopolysaccharide).[5,6]

Access this article online

Website: www.ujds.in

Quick Response Code

DOI: https://doi.org/10.21276/ujds.2025.v11.i2.18

This review has elucidated the structure as well as signaling of inhibitors targeting TLRs feedback regulators and pathway of TLR signaling. Furthermore, this review elucidated the province of TLRs in oral carcinogenesis and various diseases.

Functions of TLRs[7,8]:

1. Identification of self antigens
2. Identification of Non-self antigens

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Received : 13 August, 2024, **Published :** 30 June, 2025

How to cite this article: Himanshu Singh, Goyal, A., Sharma, S., Roy, R., Gaurav Pratap Singh, & Vaishali Malik. (2025). Toll-Like Receptors : Structure, Signaling, and Role in Oral Carcinogenesis and Various Diseases : A Narrative Review. UNIVERSITY JOURNAL OF DENTAL SCIENCES, 11(2).

3. Coupling the adaptive and innate immunity
4. Unmasking the invading pathogens
5. Management of production, survival and proliferation of cytokines.

Discovery of TLRs:

Toll-like receptors are so named because of their similarity to the proteins encoded by the Toll genes recognized by Christiane Nusslein-Volhard in 1985 in Drosophila embryonic development. She exclaimed, "That's great!" Therefore, this protein was called "Toll".[9,10]

PRRs (Pattern recognition receptors):

Microorganisms have obtained a vast array of PAMPs (pathogen-associated molecular patterns) that are remembered by innate immune cells. This 'foreign' code identification evolves through host PRRs.[11] TLRs are associated with PRR and are relevant for stability of host against microbial infection.[12] Pattern recognition receptors (PRRs) recognized DAMP and PAMP.[13]

Structure and characterization of Toll like receptors (TLRs):

TLRs have 20 to 27 extracellular LRRs that distinguish transmembrane domains, PAMP and DAMP, and IL-1 receptor domains. The extracellular domain is composed of glycan units that serve as sites for ligand binding .[14]

Constitutent of TLR family:

10 human Toll-like receptor subtypes have been identified along with 13 murine subtypes. They are expressed on numerous types of innate immune cells including mast cells, dendritic cells, basophils, macrophages, neutrophils, natural killer (NK) cells and eosinophils.[15,16] PAMP (molecular patterns associated with foreign pathogen.[17,18]

Functionally, TLRs are divided into her two types, plasma membrane and intracellular TLRs. Plasma membrane TLRs are found on the expanse of cells. Intracellular Toll-like receptors are restricted to endosomes, endoplasmic reticulum, and lysosomes.[15,17,1]

Adaptor proteins for signaling of Toll like receptors:

In mammals, 5 distinct types of signaling adaptor proteins are there.[19,20] These are

1- TIRAP/MAL (TIR domain-containing adaptor protein)
2- MyD88 or Myeloid differentiation primary-response protein 88
3- TRAM or TRIF-related adaptor molecule
4- TRIF or TIR domain-containing adaptor protein inducing IFN-β
5- SARM or Sterile α- and armadillo-motif-containing protein

Activation of TIRAP is reliant on basic MyD88 and is analogous to TLR4 and TLR2.[21,22] The MyD88 signaling cascade is required for TLR2, TLR5,TLR8,and TLR9.[23,24] The TRIF-associated adapter molecule intercede signaling of TLR4 in a TRIF-dependent or MyD88-independent manner.[25,26] SARMs serve as negative regulators of TRIF, thus regulate TLR3 and TLR4 signaling.[27]

Method of synthesis of TLR:

All Toll-like receptors receive a identical domain organization as they are all type I transmembrane proteins [28,29] TLRs are coordinated in mammalian ER (endoplasmic reticulum) and are trafficked to endosomes or the plasma membrane. Documentation aiding the crucial province of the endoplasmic reticulum in the synthesis of Toll-like receptors comes from studies on proteins Unc93B1, PRAT4A, and gp96.[30,31]

Gp96 associates with the Hsp90 protein, which controls the function and folding of integrins, immunoglobulin chains and Toll-like receptors. All toll-like receptors except TLR3 fail to function in her Gp96 in deficient macrophages. Cells lacking PRAT4A lack functional Toll-like receptors other than TLR3. Unc93B1 binds to endosomal TLRs in ER and assists in their proper folding.[32] Unc93B1 is already folded and remains bound to the toll-like receptor. This is necessary for maintaining stability of TLRs after synthesis. After contents of Unc93B1 and Toll-like receptors pass through the Golgi complex, communication between the AP-4 transport adapter and Toll-like receptors disrupts the coordination between trafficking of all Toll-like receptors.[33,34]

Exogenous and Endogenous ligands of TLRs:

PAMPs are isolated from microorganisms such as zymosan from yeast, proteins (flagellin from flagellum) and

peptidoglycan from Gram positive bacteria, lipopeptides, lipoarabinomannans, and lipoglycan from mycobacteria. It consists of structures.[35,36] Host-derived DAMPs, or endogenous ligands, are commonly formed by cell death (non-physiological) and injury and include core proteins, components of extracellular matrix (fibrinogen and hyaluronic acid), and damage to organelles and extracellular matrix components [38]

Importance of TLRs:

1. Toll-like receptors are coupling molecules. Toll-like receptors identify the pathogen and transmit signal to the antigen which destroy microbes by the process of phagocytosis.[39,40]
2. Toll-like receptors derive their utility from their ability to distinguish between DAMPs and PAMPs to induce tissue repair. The relatedness of TLR1, TLR2, and TLR6 derives from their potential to distinguish between glycolipids and bacterial lipoproteins. TLR7, TLR8 and TLR9 recognize nucleic acids. TLR5 determines bacterial flagellin. TLR4 determines fibronectin. TLR11 and TLR12 determine profiling.[41,42]
3. Toll-like receptors activate the apoptosis. It acts by pausing the synthesis of protein, confines the infection, and decreases the response of immune system.[43]
4. Toll-like receptors are considered a significant risk factor in occurrence of various diseases and modulation of signaling is recommended in the regulation of disease various therapy. For example, TLR3, TLR7, and TLR8 have pivotal roles in determination of substances causing allergic reactions.[44,45]

TLRs and Oral Carcinogenesis:

After summarizing scientific studies, large numbers of Toll-like receptors have been found and united with possibility of OSCC(oral squamous cell carcinoma). A first step in identifying an association between Toll-like receptors and oral carcinogenesis was observed by postulating the presence of apoptotic and inflammatory cells in cancer patients. The data suggest that neutrophils indicate that TLR2 and TLR6 regulate apoptotic pathways.[46]

In a study done by Park, they observed that TLR2 to TLR 5,and TLR7 were observed in cells of oral cancer. These observations suggested that stimulation of Toll-like receptors may have prognostic importance for tumorigenesis.[47]

TLR 9:

After extensive literature review, TLR9 was found to be an optimally designed receptor expressed in oral cancer. TLR9 affiliated to the IL1 receptor super family.[48] TLR9 has been observed to be most frequently expressed in many cancer specimens.[49] Higher expression of Toll like receptor-9 was observed in moderately and well-differentiated SCC.[50] Moderate to low expression of Toll like receptor-9 was observed in poorly differentiated SCC. It was observed that tumors with deeper invasion had higher expression of TLR9.[51,52]

TLR 2:

TLR2 is the second most studied Toll-like receptor for oral cancer. According to Ng et al, they find that in oral dysplasia and oral carcinoma the immune cells shows TLR2 .[53] In the tumor environment, absolute TLR2 expression indicates immune response activation contrary to neoplastic cells. Hussaini et al identified the same in their study.[54]

TLR3:

Toll like receptor-3 is immensely expressed in oral SCC. NF-κB promotes her HIF-1 expression through activation of TLR3.In vivo, TLR3 activation was united accompanying tumor growth suppression in oral SCC.[55,56] Patients with stage III tumors had poorer survival when the TLR3 genotype was mutated.[57,58]

TLR4:

By secreting anti-apoptotic proteins, TLR4 supports oral carcinogenesis. Therefore, oral SCC shows immense expression of TLR4. According to Ren et al. Patients show short survival when high TLR4 levels are present. Furthermore, Ren et al. observed immense expression of TLR4 in patients with oral SCC. High expression of TLR4 was observed in cases of moderately differentiated SCC and well-differentiated SCC. High TLR4 expression was associated with deeper tumor invasion.[59,60]

TLR5:

TLR5 suggests an association between cancer and bacteria.TLR5 participates in the identification of bacterial flagella and can increase the growth of the tumor by utilizing inflammation-dependent mechanisms. TLR5 activation leads to invasion of cancer and successive release of cytokine. Hence, the expression of TLR5 is associated with pathogenic bacterial and viral compounds following carcinogenesis in the oral cavity.[61]

TLR7:

Up-regulated expression of TLR7 was seen in oral carcinogenesis by immunohistochemical staining. Patients show poor prognosis when tumor cells show high TLR7 expression. In fibroblast-like cells, high TLR7 expression shows a better prognosis and no metastasis of lymph node.[62]

Association of Toll like receptors in various diseases

SLE (Systemic lupus erythematous):

It is observed that TLR 7 and TLR9 are seen to be immensely expressed in systemic lupus erythematous.[63,64]

Rheumatoid arthritis (RA):

Due to Toll-like receptor signaling, bacterial DNA was noticed in joints of those patients having rheumatoid arthritis which results in severe synovial inflammation.[65] TLR2 and TLR4 are highly expressed by cells which are present inside the inflamed joints.[66,67]

Behcet's disease:

Higher expression of TLR4 and TLR2 is seen in patients having active Behcet's diseases.[68]

Chronic hepatitis B virus (HBV):

Lu et al in their study observed that increased expression of TLR4 and TLR2 in peripheral blood advances the chronic HBV infection progression.[69]

Cancer:

It has been observed that TLR3, TLR2, TLR4, TLR6, and TLR9 are participating in the development of hepatocellular carcinoma. TLR1, TLR2, TLR3 and TLR4 are involved in colon cancer. TLR3, TLR4 and TLR9 is also highly expressed in breast cancer patients.[70,71]

Alzheimer's disease:

According to Zhang et al, patients of Alzheimer's disease show an apparent elevation in TLR2 and TLR 4 expression in late-onset Alzheimer's diseases.[72]

Conclusion:

Based on current scientific literature, it is determined that Toll-like receptors are important components of immune system. Targeting of Toll-like receptors signaling serve as a new confront for treatment of various diseases. In the past years, tremendous development has been seen in knowledge of signaling pathways of TLRs.. Negative regulators of TLRs signaling have been identified and their usefulness in prevention of auto-immune diseases is identified.

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