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Introductory Chapter: Toll-Like Receptors

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1. The first line of defense is filled with a variety of pattern recognition receptors

Pattern recognition receptors (PRRs), which are germ line-encoded receptors, probably provided the host with the best possible innate property to identify “nonself” invaders from both exogenous and endogenous sources. PRRs can discriminate self-microorganisms and molecules from nonself ones through recognizing conserved parts of microorganisms—which are known as microorganism-associated molecular patterns (MAMPs). If it is nonself, then they will direct the induction of inflammatory responses. In addition, PRRs allow the innate immunity to identify endogenous danger signals—which are released by stressed, damaged, or dying cells and known as damage-associated molecular patterns (DAMPs)—and thereby help in initiation of sterile inflammation. In this manner, PRRs participate in the clearance of invading pathogens by regulating infectious inflammation and contribute to tissue repair and regeneration in addition to elimination of autoimmunity and tumorigenesis by regulating sterile inflammatory processes.

They display three types of localization. Toll-like receptors (TLRs) are a kind of PRRs located in the membrane along with C-type lectin receptors. Also, nucleotide oligomerization domain (NOD)-like receptors (NLR) and retinoic acid-inducible gene I (RIG-I)-like receptors (RLR) are found in the nucleus and contribute to recognition of intracellular microorganisms. Finally, there are some proteins that their synthesis occurs in the cells and can be used as receptors by various microorganisms. TLRs—which are the subject of this book—were the first discovered family of PRRs.

2. Toll-like receptors

They exist in mammals and insects and mediate actions essential to achieve control over immune homeostasis. The major cells expressing TLRs are antigen-presenting cells (APCs). Activation of TLRs in APCs can affect maturation of these cells and T helper 1 (Th1) cell differentiation for processing more specific immune mechanisms [1]. However, different cell types of the body have the capacity to induce the expression of TLRs, allowing them to carry TLR-mediated signaling pathways and production of inflammatory mediators and type I interferons (IFN). When handling a number of immune and inflammatory pathways, TLRs are able to have a role in the induction of innate immune responses and to link the innate immunity with the acquired immunity. Interfering with TLR function leads inevitably to immunological anomalies seen in common conditions ranging from immunodeficiency and infection to allergy, autoimmunity, cancer and more generally to diseases of many organ systems including the central

nervous system, lung, cardiovascular system, kidney, skin, and gastrointestinal system which are rooted in chronic inflammation. This has been fuel for advances in prophylactic and therapeutic applications of TLRs, especially in the last two decades.

2.1 Cells expressing TLRs

TLRs are found on the different cells of both the innate and adaptive immunity. Notably, they are expressed by nonimmune cells in the body. Normal non-transformed cells, such as endothelial cells, epithelial cells, fibroblasts, glial cells, neurons, and neural progenitor cells, as well as transformed cells of the body, i.e., cancer cells, may mediate the expression of TLRs. In humans, intestinal epithelial cells (IECs) are the main nonimmune source of TLRs. It is not aimless—there is evidence that the recognition of commensal bacteria by TLRs is required for the regulation of intestinal homeostasis [2].

2.2 Structure of TLRs

To date, 13 TLRs have been described in mammals, 10 of which are present in humans (TLR1–10). Each TLR consists of three domains: intracellular, transmembrane, and extracellular. The intracellular or cytoplasmic domain is conserved between TLRs and interleukin-1 family of receptors (IL-1R). It is, thus, referred to as the Toll-IL-1R (TIR) domain. The extracellular domain includes tandem leucine-rich repeats (LRRs), which with their curved surface appear to determine which ligand(s) a TLR can bind. The transmembrane location of TLRs makes them very suitable to transmit signals from the extracellular matrix to the cytoplasm (signal transduction).

2.3 Cellular distribution of TLRs

TLRs are located either within the cell membrane or in the intracellular compartments including the endoplasmic reticulum, endosomes, lysosomes, and endolysosomes:

Cell-membrane TLRs: TLR1, TLR2, TLR4, TLR5, TLR6, and TLR10

Intracellular TLRs: TLR3, TLR7, TLR8, and TLR9

Like other receptors, TLRs act in relation to their cellular distribution. Cell-membrane TLRs are eligible for identification of membrane components of microorganisms, e.g., lipids, proteins, and lipoproteins, while intracellular TLRs are for identification of nuclear components of microorganisms, i.e., nucleic acids.

2.4 Ligands of TLRs

In general, MAMPs are divided into three: glycans, proteins, and nucleic acids. Particularly, ligands that participate in host-pathogen interactions vary based on the pathogen identity and include:

Bacteria: lipoteichoic acid, peptidoglycan, lipoprotein/lipopeptides, deoxyribonucleic acid (DNA), flagellin, and lipopolysaccharide

Viruses: coat proteins and nucleic acids

Parasites: glycosylphosphatidylinositol (GPI) protein-membrane anchors

Yeast: zymosan

	Cellular distribution [3]	Expressing cell type				Exogenous ligands [4]			
		Innate immune cells	Adaptive immune cells	IECs	Cancer cells	Bacteria Ligand (origin)	Viruses Ligand (origin)	Fungi Ligand (origin)	Protozoa Ligand (origin)
TLR1	Cell surface	Monocyte/macrophage Neutrophils MDCs PDCs	B cells	×	×	Lipopeptides Soluble factors (<i>N. meningitidis</i>)	×	×	×
TLR2	Cell surface	Monocyte/macrophage Neutrophils MDCs Mast cells	×	×	Gastric cancer Colorectal cancer Ovarian cancer Cervical cancer Lung cancer Melanoma Brain cancer Breast cancer Liver cancer Laryngeal cancer Pancreatic cancer	Lipoprotein/lipopeptides (GPB, mycoplasma, mycobacteria, Spirochetes) Peptidoglycan (GPB) Lipoteichoic acid (GPB) PSM (<i>S. epidermidis</i>) HKB (<i>L. monocytogenes</i>) Porins (<i>Neisseria</i>) Soluble factors (<i>N. meningitidis</i>) Atypical LPS (<i>L. interrogans</i> , <i>P. gingivalis</i>) OmpA (<i>K. pneumoniae</i>) Glycolipids (<i>T. maltophilum</i>) LAM (mycobacteria)	HA (MV) SVP (HSV, CMV)	Zymosan (<i>Saccharomyces</i>) PLM (<i>C. albicans</i>)	GIPLs (<i>T. cruzi</i>)

	Cellular distribution [3]	Expressing cell type				Exogenous ligands [4]			
		Innate immune cells	Adaptive immune cells	IECs	Cancer cells	Bacteria Ligand (origin)	Viruses Ligand (origin)	Fungi Ligand (origin)	Protozoa Ligand (origin)
TLR3	Intracellular endosomal compartment	MDCs	B cells T cells	×	Colorectal cancer Ovarian cancer Cervical cancer Lung cancer Melanoma Breast cancer Liver cancer Laryngeal cancer	×	dsRNA	×	×

	Cellular distribution [3]	Expressing cell type				Exogenous ligands [4]			
		Innate immune cells	Adaptive immune cells	IECs	Cancer cells	Bacteria Ligand (origin)	Viruses Ligand (origin)	Fungi Ligand (origin)	Protozoa Ligand (origin)
TLR4	Cell surface	Monocyte/macrophage Neutrophils MDCs Mast cells	B cells	✓	Gastric cancer Colorectal cancer Ovarian cancer Cervical cancer Lung cancer Prostate cancer Melanoma Brain cancer Breast cancer Liver cancer Laryngeal cancer	LPS (GNB) Hsp60 (<i>C. pneumonia</i>)	Envelope proteins (RSV and MMTV) Fusion protein (RSV)	×	GIPLs (<i>T. cruzi</i>)
TLR5	Cell surface	Monocyte/macrophage Neutrophils MDCs	×	✓	Breast cancer Gastric cancer Colorectal cancer Ovarian cancer Cervical cancer	Flagellin (flagellated bacteria)	×	×	×

	Cellular distribution [3]	Expressing cell type				Exogenous ligands [4]			
		Innate immune cells	Adaptive immune cells	IECs	Cancer cells	Bacteria Ligand (origin)	Viruses Ligand (origin)	Fungi Ligand (origin)	Protozoa Ligand (origin)
TLR6	Cell surface	Monocyte/macrophage Neutrophils Mast cells MDCs PDCs	B cells	×	Liver cancer	Diacyl lipopeptides (mycoplasma) Lipoteichoic acid (GPB) PSM (<i>S. epidermidis</i>) HLSF (group B streptococcus)		Zymosan (<i>Saccharomyces</i>)	
TLR7	Intracellular endosomal compartment	Monocyte/macrophage Neutrophils DCs	B cells	×	×	×	ssRNA	×	×
TLR8	Intracellular endosomal compartment	Monocyte/macrophage Neutrophils MDCs Mast cells	×	✓	×	×	ssRNA	×	×
TLR9	Intracellular endosomal compartment	Monocyte/macrophage Neutrophils PDCs	B cells T cells	×	Gastric cancer Colorectal cancer Cervical cancer Lung cancer Prostate cancer Breast cancer Liver cancer	Unmethylated CpG DNA	Unmethylated CpG DNA	×	Hemozoin (<i>Plasmodium</i>)

	Cellular distribution [3]	Expressing cell type				Exogenous ligands [4]			
		Innate immune cells	Adaptive immune cells	IECs	Cancer cells	Bacteria Ligand (origin)	Viruses Ligand (origin)	Fungi Ligand (origin)	Protozoa Ligand (origin)
TLR10	Cell surface	Monocyte/macrophage	B cells	✓	×	Triacylated lipopeptides	×	×	×

GPB, gram-positive bacteria; IEC, intestinal epithelial cells; LPS, lipopolysaccharides; OmpA, outer membrane protein A; HSV, herpes simplex virus; CMV, cytomegalovirus; GPIs, glycoinositolphospholipids; dsRNA, double-stranded RNA; GNB, gram-negative bacteria; DCs, dendritic cells; MMTV, mouse mammary tumor virus; RSV, respiratory syncytial virus; ssRNA, single-stranded RNA; MDS, myeloid dendritic cells; N. meningitides, Neisseria meningitides; PDCs, plasmacytoid dendritic cells; S. epidermidis, Staphylococcus epidermidis; PSM, phenol-soluble modulins; HKB, heat-killed bacteria; L. monocytogenes, Listeria monocytogenes; L. interrogans, Leptospira interrogans; P. gingivalis, Porphyromonas gingivalis; K. pneumoniae, Klebsiella pneumoniae; T. maltophilum, Treponema maltophilum; LAM, lipoarabinomannan; PLM, phospholipomannan; T. cruzi, Trypanosoma cruzi; C. albicans, Candida albicans; HA, hemagglutinin; MV, measles virus; SVP, structural viral proteins; C. pneumonia, Chlamydia pneumonia; HLSF, heat-labile soluble factor.

Table 1.

Toll-like receptors: cellular distribution, expressing cell types, and exogenous ligands.

TLRs have been reported to bind endogenous and exogenous ligands. There is a wide range of microorganisms including bacteria, viruses, protozoa and helminth parasites, and fungi that TLRs can defend against. **Table 1** provides an overview of ligands and associated pathogens that interact with TLRs. However, below are representative examples for MAMPs that can be recognized by TLRs:

TLR1: lipoproteins

TLR2: lipoteichoic acid, peptidoglycan, lipoproteins, and zymosan

TLR3: viral dsRNA

TLR4: lipopolysaccharide, viral envelope protein, and viral fusion protein

TLR5: flagellin

TLR6: lipoteichoic acid, lipoproteins, and zymosan

TLR7 and TLR8: viral ssRNA, synthetic antiviral compounds (imidazoquinolines)

TLR9: bacterial and viral DNA

TLR10: triacylated lipopeptides

Endogenous ligands that can be recognized by TLRs are numerous but mainly include extracellular matrix components, high-mobility group box 1, heat shock proteins (HSP), tenascin-C, cardiac myosin, and S100 proteins (for review see [5]).

3. TLR-mediated signaling pathways: network of adaptor molecules and transcription factors

Ligand recognition by TLRs involves the recruitment of different TIR domain-containing adaptor proteins. The types of adaptor proteins they use at least in part explain distinct functions of TLRs.

To date, there have been four adaptor proteins found to interact with specific TLRs (**Table 2**). Myeloid differentiation primary response 88 (MyD88) was the first of its kind. It is an intracytoplasmic adaptor molecule that consists of a C-terminal TIR domain and an N-terminal death domain. Its TIR domain—which is fundamental to ligand site recognition—can interact with all TLRs with the exception of TLR3. Recruitment of MyD88 by TLRs initiates the cascades of mitogen-activated protein kinases (MAPKs) and nuclear factor- κ B (NF- κ B) that result in the production of inflammatory cytokines.

In this context, TIR-domain-containing adapter-inducing interferon- β (TRIF) is another adaptor protein. TLR3 and also TLR4 can act as a trigger for TRIF-dependent signaling. This signaling then utilizes transcription factors NF- κ B and interferon regulatory factor 3 (IRF3) to produce inflammatory cytokines and type I IFN.

Toll-interleukin 1 receptor (TIR) domain-containing adaptor protein (TIRAP) and TRIF-related adaptor molecule (TRAM) are last two remaining TIR domain-containing adaptor proteins. They are specialized for directing other adaptors to specific TLRs and thus are referred to as sorting adaptors. TIRAP serves as the sorting adaptor for MyD88 and facilitates its recruitment to TLR1, TLR2, TLR4, and TLR6, while TRAM is merely involved in the interaction between TRIF and TLR4.

In this manner, the discussion on signaling pathways mediated by TLRs is commonly held in MyD88-dependent and TRIF-dependent settings (for review see [7]). **Figure 1** is a schematic diagram of TLR location and pathways.

	Signaling adaptor(s)			Transcription factor(s)	Products	
	MyD88-dependent signaling	TRIF-dependent signaling	Sorting adaptor		Inflammatory cytokines	Type I IFN
TLR1	✓	×	TIRAP	NF-κB	✓	×
TLR2	✓	×	TIRAP	NF-κB	✓	×
TLR3	×	✓	×	NF-κB, IRF3, and IRF7	✓	✓
TLR4	✓	✓	TIRAP and TRAM	NF-κB, IRF3, and IRF7	✓	✓
TLR5	✓	×	×	NF-κB	✓	×
TLR6	✓	×	TIRAP	NF-κB	✓	×
TLR7	✓	×	×	NF-κB and IRF7	✓	✓
TLR8	✓	×	×	NF-κB and IRF7	✓	✓
TLR9	✓	×	×	NF-κB and IRF7	✓	✓

Table 2.
 Toll-like receptor: signaling pathways and products [6].

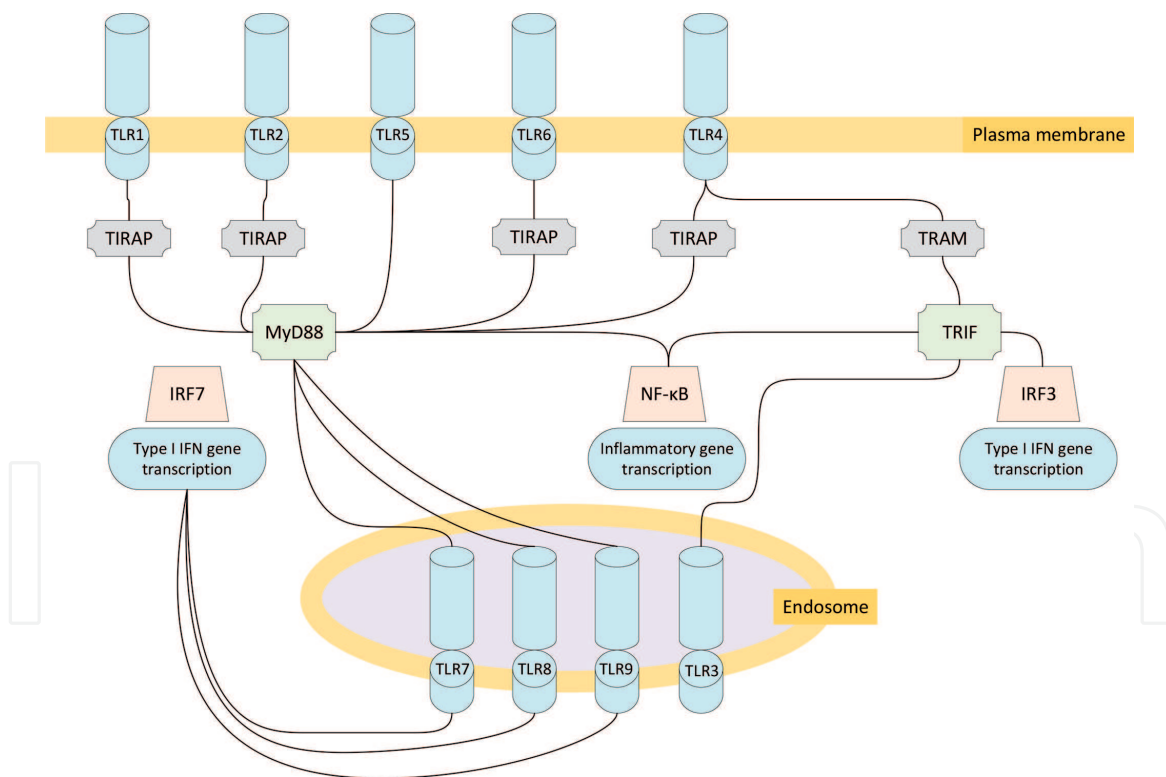


Figure 1.
 Toll-like receptor (TLR) location and signaling pathways.

3.1 TLRs and different disease entities

Studies in mice have demonstrated that TLR signaling change underlies a range of pathologies. Supporting this, human studies propose that single nucleotide polymorphisms (SNPs) that alter—whether upregulated or downregulated—TLR signaling may predispose to or protect from development of diseases [8].

3.2 Autoimmunity

All 10 TLRs that are present in humans (except to TLR5) have been associated with autoimmune and inflammatory diseases including arthritis, systemic lupus erythematosus, scleroderma, and Sjogren's syndrome [9]. There are potential opposing views on involvement of TLRs in autoimmunity.

Autoimmunity is referred to as conditions where the immune system is fighting against the body itself by production of antibodies, the so-called autoantibodies, against self molecules, the so-called autoantigens. Autoantibodies bind to autoantigens and form immune complexes. The cytokine interferon-alpha (IFN α) was first thought to have a pure white role of antiviral immunity. However, the observations of autoimmune features caused by the use of recombinant IFN α in patients with chronic viral infections have expanded the former function of IFN α far beyond antiviral immunity to autoantibody production and autoimmunity. A hypothesis is that immune complexes having nucleic acids can act as ligands for TLRs, thereby making the innate immune cells to induce more than wanted or unwanted responses. TLRs that can recognize nucleic acids, i.e., TLR7 and TLR9, and plasmacytoid dendritic cells (pDCs) that express these receptors and produce IFN α in response are of particular importance in this context [9]. In contrast, some TLRs have been reported to turn the knob in the opposite direction. When reviewing the role of TLRs in inflammatory arthritis, TLRs may stimulate osteoclastogenesis, and on the other side, there are TLRs that inhibit activation of osteoclasts and thus can prevent bone destruction [10].

3.3 Brain diseases

Different brain cells reveal the expression of TLRs:

Microglia express all TLRs.

Neurons express TLR3, TLR7, TLR8, and TLR9.

Astrocytes express TLR2, TLR3, and TLR9.

Oligodendrocytes express TLR2 and TLR3.

The role of TLRs has been characterized in the normal central nervous system (CNS) as well as in disease states of the CNS. Experimental evidence suggests the possible role of TLR2 in neurogenesis, whereas TLR3 and TLR4 apparently act as downregulators of neurogenesis. Enhancement of hippocampal-dependent working memory in mice lacking TLR3 implicates this receptor as a negative regulator of cognitive functions as well. In bacterial infections of the brain and abscess formation, TLR2, TLR4, and TLR9 are essential to elicit immune responses. In the cases of viral meningitis, TLR3 and TLR9 engagement can help to localize infection and diminish neural injury as well. In parasite infections of the brain, TLR1, TLR2, and TLR9 show paradoxical effects—they may worsen disease rather than clear parasites from the brain. Both models of neuronal injury and of spinal cord injury indicate a role for TLR2 and TLR4 in inducing neuronal death and axon and myelin damage. Finally, evidence points to the potential role that TLR2, TLR4, TLR5, TLR7, and TLR9 can play in preventing the accumulation of amyloid plaques and progression of Alzheimer's disease [11].

3.4 Cardiovascular diseases

Cardiac myocytes show the expression of TLR2, TLR3, TLR4, and TLR6. TLRs play paradoxical roles in different myocardial diseases. For example, TLR2 was

shown to mediate apoptosis of cardiac myocytes induced by hydrogen peroxide and doxorubicin, while TLR4 attenuated apoptosis of cardiac myocytes. Targeting both TLR2 and TLR4 provided protection in septic cardiomyopathy. TLR4 blockade implied benefit to ischemia-reperfusion injury and cardiac hypertrophy as well (for review see [12]).

TLR4 is also said to be highly expressed in atherosclerotic lesions which inflammation is supposed to incorporate in its nature. There are possible explanations which can be given to this fact. The oxidization of lipids as a way to form atherosclerotic lesions accompanies thermal stress through HSP production. Oxidized lipids and HSPs can act as ligands and upregulate MyD88-dependent TLR4 relevant to inflammatory cytokine production. Another explanation is that TLR4 mediates recognition of *Chlamydia pneumoniae*, which in turn is closely related to atherosclerosis. In this manner, it would be understandable that individuals carrying Asp299Gly and Thr399Ile—which interfere with TLR4 function—develop less atherosclerotic vascular events, such as carotid stenosis, acute coronary events, acute myocardial infarction, diabetic neuropathy, and allograft rejection [13]. On the other hand, TLRs, in particular TLR2, TLR4, TLR7, and TLR9, by the aid of adenosine, can succeed in angiogenesis after myocardial injury [12].

3.5 Infections

As described above, TLR4 is critical in recognizing LPS of gram-negative bacteria (GNB). People's reactions are different to LPS inhalation and range from tolerance, i.e., no reaction, to strong asthma-like reactions. SNPs of human TLR4 gene, i.e., Asp299Gly and Thr399Ile, have been reported to affect the degree of reaction to LPS among healthy subjects and allergic asthmatic patients, development of septic shock by GNB, incidence of severe respiratory syncytial virus (RSV) bronchiolitis, risk of GNB colonization and of premature birth in pregnant women, and incidence of infections by GNB in patients on an intensive care unit [13].

3.6 Kidney diseases

Less is understood about the role of TLRs in kidney diseases. However, experimental evidence suggests that all TLRs are involved in sepsis and renal infections. Each TLR has its own associations with distinct renal diseases as well (for review see [14]).

3.7 Liver diseases

In the liver, TLR expression is observed on a variety of cells including Kupffer cells (TLR2, TLR3, TLR4, and TLR9), hepatocytes (all TLRs), hepatic stellate cells (TLR2, TLR4, and TLR9), biliary epithelial cells (TLR2, TLR3, TLR4, and TLR5), sinusoidal epithelial cells (TLR4), hepatic dendritic cells (TLR2, TLR4, TLR7, and TLR9), hepatic natural killer cells (TLR1, TLR2, TLR3, TLR4, TLR6, TLR7, and TLR9), and hepatic B cells (TLR2, TLR4, TLR7, and TLR9). Undoubtedly, such widely distributed TLRs have been an important part of multiple liver diseases including infections of the liver by *L. monocytogenes*, and *S. typhimurium*, *P. falciparum*, hepatitis C virus, and hepatitis B virus, alcohol-induced liver diseases, nonalcoholic fatty liver disease, hepatic fibrosis, liver injury, liver regeneration, and hepatocellular carcinoma, and hepatic immune disorders (for review see [15]).

3.8 Malignancies

As for other sections, TLRs present positive and negative effects in tumorigenesis which have been discussed in [16].

3.9 Other diseases

The possible role of TLRs in periodontal health, lung diseases, and dermatological diseases has been reviewed in detail elsewhere [17–19].

4. Clinical implications

4.1 TLR agonists

TLR agonists have offered to help boosting the immune responses to vaccination as well as potential for immunotherapy of cancer, allergy, and infections. Three of which have received approval by the Food and Drug Administration (FDA) and are listed here:

Bacillus Calmette-Guérin (BCG) can act as an agonist of TLR2/TLR4 and be used for treatment of superficial transitional cell carcinoma of the bladder. Monophosphoryl lipid A (MPL) can cause activation of TLR2/TLR4 recommended for the prophylaxis of human papilloma virus (HPV)-associated cervical cancer.

Imiquimod functions as a TLR7 agonist with implications for the treatment of actinic keratosis, basal cell carcinoma, and genital and perianal warts [20].

4.2 TLR antagonists

Antagonists targeting TLR-mediated signaling have displayed anti-inflammatory features that may be effective against invading pathogens and autoimmune diseases.

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