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REVIEW

Toll-like receptors targeting technology for the treatment of lymphoma

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ABSTRACT

Introduction: The crucial role of Toll-like Receptors (TLRs) in innate and adaptive immune systems is well discussed in the literature. In cancer, TLRs act as a double-edged sword that can promote or suppress tumor growth.

Areas covered: In this article, the authors uncover the potential role of TLRs in lymphomas, which are cancers related to the lymphatic system and blood cells. TLRs are *de facto* inflammation-inducing receptors that can either worsen disease or ameliorate lymphoma treatment. From this perspective, the usage of TLRs to modulate the immune system toward lymphoma regression is desirable. Various strategies have been used so far, and novel ways are being sought out to cure lymphoma.

Expert opinion: TLR ligands have successfully been used to improve patient health; however, these receptors must be finely tuned to further optimize therapy. For a better outcome, novel specific ligands, improved pharmacodynamics, and unique targets should be discerned. Ligands with conjugated molecules, nanoparticles, and targeted drug delivery can highly optimize the therapy for lymphoma with various etiologies.

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1. Introduction

The term 'lymphoma' refers to a group of tumors affecting blood cells that are involved in the immune system and lymphoid tissues [1]. Signs and symptoms include fever, fatigue, itching, weight loss, drenching sweats, and enlarged lymph nodes. The most prevalent type of lymphoma (more than 80% of cases) originates from B lymphocytes, which are involved in producing antibodies against various infections [1]. Broadly, lymphoma can be categorized into two major groups: Hodgkin lymphoma (HL), which is a cancer of blood cells and bone marrow, and non-Hodgkin lymphoma (NHL) that affects the lymphatic system, another branch of the circulatory system. In addition to these two types, other lymphoma categories include NHL in children and in skin, and Waldenstrom macroglobulinemia. NHL is most common blood-related cancer worldwide comprising 40 various types [2]. Furthermore, these types of lymphoma are subdivided based on their cell type of origin (natural killer [NK] cells, T cells, or B cells), pathogenomics, and their expression of various molecular markers, and these cancers have been comprehensively categorized by the World Health Organization (WHO) [3]. The subdivision of lymphoma into over 50 types by the WHO classification system is based on the morphology, genetic features, and identification of specific proteins present on lymphoma cell surfaces [3]. This extensive lymphoma classification can be useful to promote scientific development regarding etiology, treatment, basic research, and drug discovery for developing novel biological insights that may lead to more focused treatment.

In a recent study, frequencies of NHL in the developing countries are evaluated and compared with the developed regions of the world. With the help of WHO, 4848 lymphoma cases from 25 different countries have been studied, whereas, among these, 93.6% cases were confirmed as NHL with higher rate in males from developing countries. During 2016, the estimated incidence of new lymphoma cases is greater than 81,000. The incidence rate of previous years is very hopeful. For example, since 2001–2007, HL incidence rate has been increased, whereas it has been reduced by 2.4% from 2008 to 2012. According to an estimate by American Cancer Society, in 2016 alone, the number of deaths due to lymphoma will be above 21,000 and in these deaths, NHL will be the major contributor. From 2003 to 2012, the mortality rate due to NHL has been decreased by 2.5% per year, which may reflect the improvement in the treatment methodologies [4].

Determining the specific molecular signaling pathways that serve as the driving force for the development and growth of tumor cells lead to targeted drug development. Because aiming at critical points in essential pathways is thought to be an effective strategy, this approach has been adopted by several studies to find potential drug targets [5]. From the drug discovery and development perspective, targeted therapies have proven to be rational targets and good starting points for treatment. Some proteins can be targeted with small molecules that act as agonists or antagonists, a well-known concept of protein pathway manipulation, and these targets are termed as 'druggable' [5]. Hence, screening for druggable targets in pathways that drive tumor proliferation can lead to the targeted and focused drug therapy with fewer side effects. Imatinib, tyrosine kinase inhibitor, is a very prominent example of the success of this strategy [6]. It has been developed as the

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Article highlights

- Lymphoma is a proliferative disorder that mainly affects blood cells and these cells are vital for the immune system by expressing TLRs
- TLRs act as a double-edged sword regarding tumor progression as well as regression in lymphoid malignancies
- TLRs ability to enhance tumor antigen presentation has rendered them as potential therapeutic agents
- TLR ligands with tumor-promoting properties should be carefully utilized for therapeutic purposes
- Therapeutic efficacy can be improved through various mechanisms associated with TLR biological processes
- In cancer, recurrence has several causes and is a major problem. To completely eradicate cancer cells, it is imperative to treat patients with a combination of drugs. Combinatorial therapy has a higher chance to suppress the disease and prevent its recurrence.

This box summarizes key points contained in the article

selective inhibitor of BCR-Abl tyrosine-kinase, in Philadelphia positive chronic myelogenous leukemia (CML) [7]. This chimeric kinase initiates and maintains the CML by triggering multiple downstream pathways that result in mitogenic signaling activation, altered cellular adhesion, and inhibition of apoptosis. BCR-Abl-mediated signaling can also have effects on DNA repair mechanism that inevitably prone the genetic material to further mutations. Imatinib has multiple descendants that have the role in various other lymphomas [7].

Toll-like receptors (TLRs) are evolutionarily conserved pathogen recognition receptors (PRRs) that play a critical role in the innate immune system of all multicellular organisms. In addition to innate immunity, TLRs play a crucial role in activating adaptive immunity by inducing secondary signals required for cell-mediated and humoral immunity [8,9]. In mammals, there are 13 TLR family members [10–15] that are primarily expressed on immune cells such as lymphocytes, dendritic cells (DCs), macrophages, and neutrophils [16,17]. Lymphocytes and a few other cell lineages express all TLRs, and they are also detected in other cell lineages throughout the body [18]. These lymphocytes are crucial in the adaptive immune response against infections by expressing various inflammatory molecules [16,19–21], establishing a link between the tumor and inflammation. Similarly, during prolonged microbial infections, the inflammatory response is considered the major reason for the progression and formation of indolent lymphoma. A significant relationship between B-cell lymphoma (BCL) and infections such as *Helicobacter pylori* (*H. pylori*) and Hepatitis C virus (HCV) has been reported [22,23]. During maturation, B cells express various TLRs that, in conjunction with B-cell receptors (BCRs), are responsible for initiating physiological phenomena in normal B cells such as plasma cell differentiation, anti-apoptotic effects, and proliferation [20]. Moreover, during B-cell development, TLR2 expression is limited to intermediary positive B cells (a subset of short-lived $CD19^+$ cells) where it plays a role in the formation of the B-cell zone or germinal center [24]. In tumor cells, B lymphocytes show increased proliferation in response to TLR ligands, strengthening the association between inflammation and cancer [25,26].

2. TLR structure, ligands, and signaling

TLRs are type I transmembrane receptors comprised of an ectodomain and cytoplasmic domain. Their endodomain comprises a Toll/interleukin-1 receptor (TIR) domain, whereas their ectodomain consists of a motif with leucine-rich repeats (LRRs). Cell expressing TLRs on the surface recognize bacterial and fungal ligands such as lipopeptides, lipopolysaccharides, and peptidoglycans known as pathogen-associated molecular patterns (PAMPs), whereas endosomal TLRs recognize the RNA/DNA of viral or bacterial origin [27,28]. Furthermore, a few endogenous ligands can also activate TLRs (Table 1) [29–31]. Each member of the TLR family recognizes specific ligands; however, TLR activation and signal transduction mechanisms are conserved. LRRs present in TLR ectodomains bind ligands and initiate signaling cascades through adaptor molecules such as myeloid-differentiation factor 88 (MyD88) or TIR-domain-containing adapter-inducing interferon-β (TRIF) (Figure 1).

Ligand recognition is followed by TLR dimerization, and a signaling cascade starts in the cell to activate the transcription of genes responsible for producing inflammatory molecules like chemokines, cytokines, adhesion molecules, and costimulatory molecules of DCs. Downstream signaling is perpetuated by a variety of adaptor molecules. With the exception of TLR3, all TLRs are MyD88-dependent for signal transduction, sometimes in combination with TIR domain containing adaptor protein (TIRAP), another adaptor molecule. TLR3 exclusively signals through TRIF, and TLR4 can engage TRIF from the endosome with the help of TRIF-related adaptor molecule (TRAM) as an intermediate signaling molecule [30]. However, initiation of the MyD88-dependent signaling pathway recruits interleukin 1 receptor associated kinase (IRAK) 4 through interaction with the death domain. Later, IRAK4 forms a complex with IRAK1 that leads to the auto- and cross-phosphorylation of both proteins. Tumor necrosis factor (TNF) receptor-associated factor 6 (TRAF6) is recruited to the IRAK1/4 complex, is ubiquitinated, and activates the TGF-β-activated kinase 1 (TAK1)/TAK1 binding protein 1 and 2 (TAB1/2) complex by phosphorylation of TAB2 and TAK1. The role of polyubiquitination in TRAF6-mediated TAK1 activation along with the activation of mitogen activated protein kinase (MAPK) and the inhibitor of κ-kinase (IKK) has been demonstrated in many recent studies [32,33]. Novel TRAF6-mediated Lys-63-linked polyubiquitination, linking Ubc-like protein Uev1A and ubiquitin-conjugating enzyme Ubc13, is necessary for the TAK1 activation, which leads to the activation of IKK in NF-κB pathway [34]. Activated TAK1 leads to the phosphorylation of MAPKs and the IKK complex (IKK-α, IKK-β, and IKK-γ). The IKK complex is responsible for phosphorylation of IκB, leading to its ubiquitination and subsequent degradation. Consequently, NF-κB is released and it translocates into the nucleus to initiate the transcription of target genes [30]. Signaling in MyD88-dependent and -independent modes activates different inflammatory pathways such as JNKs/AP1, IFN, and NF-κB [27,35], and these pathways result in the secretion of proinflammatory mediators, IFNs, and other cytokines that defend the host against invading pathogens.

Table 1. Toll-like receptors and lymphoma.

TLRs	Exogenous ligand	Endogenous ligand	Expression in lymphoma	TLR mutations		Therapeutic use of agonists	TLR agonist-based drugs in clinical trials
				Mutation correlation			
TLR1	Triacyl lipopeptides	NA	MCL	NA	NA	NA	NA
TLR2	Lipoproteins Lipopeptide Peptidoglycan Lipoteichoic acid Glycolipids	HSP60 HSP70 HSP96 HMGB1 Hyaluronic acid	DLBCL MALT	rs3804100 (c.1350 T > C)	Positive (MALT)	TLR2 agonist is used for HL and ALL leads to the augmentation of IL-6, IL-8, IL-10, IFN production, and CD40 expression	NA
TLR3	ssRNA and dsRNA	mRNA	DLBCL FL Peripheral T-cell lymphoma	NA	NA	TLR3 agonist is used for MM to induce apoptosis in tumor cells	*Durvalumab + Tremelimumab + poly ICLC (Phase 1/2)
TLR4	Lipopolysaccharide Fibronectin	HSPs HMGB1 protein	MALT MCL	rs4986790 (c.896 A > G)	Positive (MALT, HL)	NA	NA
TLR5	Flagellin	NA	MALT	NA	NA	NA	NA
TLR6	Diacyl lipopeptides Lipoteichoic acid	NA	DLBCL FL Peripheral T-cell lymphoma	rs5743815 (c.1280 T > C)	Positive (NHL)	NA	NA
TLR7	Viral ssRNA	Endogenous RNA	MCL DLBCL FL Peripheral T-cell lymphoma	NA	NA	TLR7 agonist is used for cutaneous T-cell lymphoma to activate NK & CD8 T cells, increase IFN production	**IMO-8400 (Phase 1/2)
TLR8	Viral ssRNA	Endogenous RNA	DLBCL	NA	NA	NA	**IMO-8400 (Phase 1/2)
TLR9	Unmethylated CpG DNA	Endogenous DNA	MCL DLBCL FL Peripheral T-cell lymphoma BL	rs5743836 (−1237 T > C) rs352140 (2848 A > G)	Positive (HL)	TLR9 agonist is used for DLBCL, BL and cutaneous T-cell lymphoma to cause cytokine expression and tumor cell death. In FL, CpG adjuvant vaccines are used to make B cells more immunogenic	**IMO-8400 (Phase 1/2) ***CpG vaccine (Phase 1)
TLR10	Unknown	NA	MCL	NA	NA	NA	NA
TLR11	Profillin-like molecule	NA	NA	NA	NA	NA	NA

*Identifier: NCT02643303; ** Identifier: NCT02252146; *** Identifier: NCT00780988.

ALL: Acute lymphoblastic leukemia; BL: Burkitt lymphoma; DLBCL: Diffuse large B-cell lymphoma; FL: follicular lymphoma; HL: Hodgkin Lymphoma; HSP: heat shock protein; HMGB1: high-mobility group box 1; IL: interleukin; IFN: interferon; MALT: mucosa-associated lymphoid tissue; MCL: mantle cell lymphoma; MM: multiple myeloma; NA: not available; NK: natural killer.

List of Toll-like receptors (TLRs), their exogenous and endogenous ligands, the expression of different TLRs, the effects of mutations in various subtypes of lymphoma, their therapeutic uses, and clinical trials of TLR ligands.

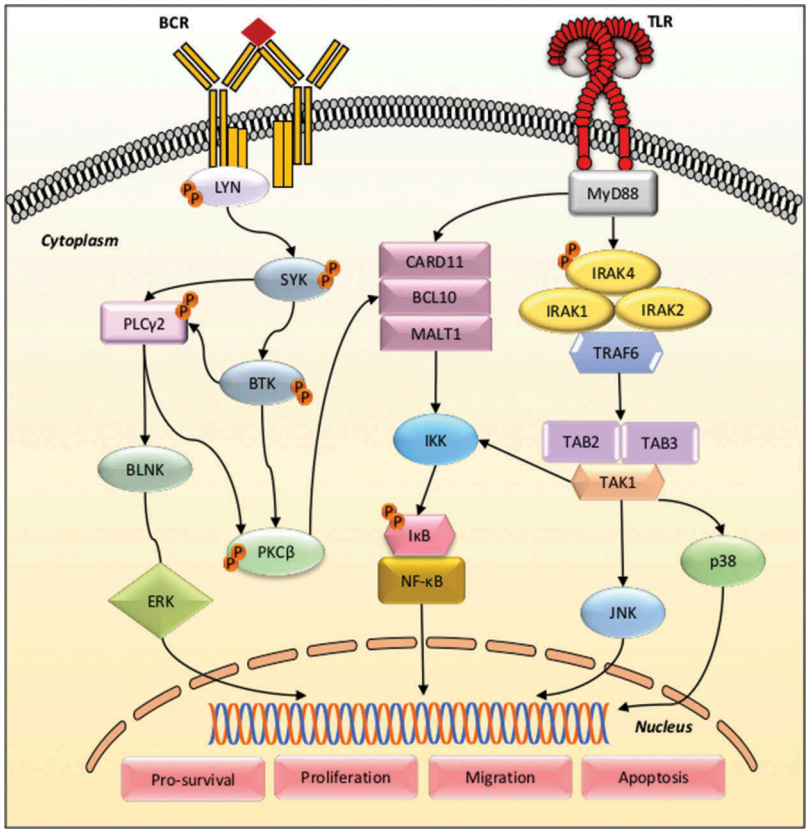

Figure 1. Overview of B-cell receptor (BCR) and Toll-like receptor (TLR) crosstalk. BCRs consist of membrane immunoglobulin molecules connected with immunoglobulin heterodimers Igα/Igβ (CD79a/CD79b). The first encounter of an antigen with a BCR leads to receptor molecule aggregation, that subsequently activates the Src family kinase v-yes-1 Yamaguchi sarcoma viral related oncogene homolog (LYN) and the Igα/Igβ subunit initiates the downstream signaling, which activates spleen tyrosine kinase (SYK) and bruton agammaglobulinemia tyrosine kinase (BTK). Activation of SYK recruits a number of additional kinases, leading to the activation of two main pathways: the BTK-mediated pathway and the phospholipase C-γ2 (PLC-γ2)-mediated pathway. Moreover, SYK and BTK both phosphorylate and activate PLC-γ2 that transduces signals through adaptor protein B-cell linker (BLNK) and ERK kinase. BTK also activates protein kinase Cβ (PKCβ), which is a crucial component in BCR signaling, which phosphorylates the CARD11-BCL10-MALT1 complex, followed by activation and recruitment of IKK that phosphorylates IκB and leads to NF-κB translocation into the nucleus. Simultaneously, activation of the TLR signaling pathway transduces signals through adaptor proteins including the interleukin 1 receptor-associated kinase (IRAK) and TNF receptor-associated factor 6 (TRAF6), and converges with the BCR pathway at NF-κB. Translocation of NF-κB into the nucleus initiates many processes determined by the antigen and the maturation state of the cell, including apoptosis, tolerance, migration, survival, and differentiation of B-cells.

3. Role of TLRs in B-cell physiology

In addition to granulocytes and monocytes, TLRs are also expressed by lymphocytes. Human-naive B lymphocytes express TLRs in very low to undetectable levels [36]. However, upon BCR stimulation following the first antigen encounter, significant levels of specific TLRs are expressed [19,21,36,37]. Certain components of bacterial cell wall activate the TLRs present on cell surface but in naive B cells, the expression of TLRs was found to be very less. In contrast, endosomal TLRs present in human naive B cells play a major role in B-cell activation by microbial nucleic acids [20]. For B-cell differentiation and proliferation, as well as the elimination of auto-reactive B lymphocytes, TLR signaling pathways are crucial [38,39]. It has been proposed in a 3-step model that co-stimulation of BCR, TLR, and CD40 is essential for naive B-lymphocyte activation and extensive proliferation [37,40]. Instead, in the absence of particular BCR ligation, TLR ligands can activate naive B-cell proliferation in combination with bacterial antigens [41]; moreover, instead of T cells, plasmacytoid-derived DCs are specialized in IFN type 1 production that may induce B-cell differentiation and proliferation through BCR and TLR9 signaling [42]. Hence, TLRs are present downstream of BCR in human B cells and are crucially involved in primary and memory immunity; however, both TLR and BCR signaling pathways converge at specific points and regulate each other's signal transduction (Figure 1) [43].

Functional and phenotypic changes induced due to targeting TLRs present on malignant B cells affect the cellular susceptibility to pharmaceutical drugs. These alterations can put upon for combined therapeutic approaches. Like, TLR9 stimulation with CpG ODN increases the CD20 expression in malignant B cells, which could be exploited to improve the efficacy of anti-CD20 monoclonal antibody rituximab [20]. It has been suggested that, in addition to certain microenvironmental elements, TLRs may also be involved in the blood-related malignancies, particularly lymphoid malignancies by different means. It includes microbial infections stimulating TLRs (in case of marginal zone lymphoma [MZL]), genetic variations in TLRs (single nucleotide polymorphisms [SNPs] in TLR2 and TLR4 cause various lymphoma), and PAMPs acting through TLRs as survival factors for myeloma cells [44].

Moreover, it has also been documented that upon ligand interaction, TLRs on T lymphocytes may directly influence T-cell

physiology. For instance, in T-cell receptor activation, TLR2/3/5 and 9 can enhance proliferation and the production of inflammatory molecules from T lymphocytes [45]. Furthermore, TLR2/5 and TLR8 regulate the suppressive activity of $CD25^+$ $CD4^+$ Treg cells.

4. TLRs and lymphoproliferative disorders

Monoclonal B lymphocyte accumulation and expansion at different maturation stages can cause lymphoproliferative disorders. These disorders can be classified based on their clinical features as indolent/chronic or aggressive. Diffuse large B-cell lymphoma (DLBCL) and Burkitt lymphoma (BL) are aggressive types of disease that undergo genetic changes, which are identified by an increased proliferation rate and are crucially involved in the pathogenesis [44]. In the case of chronic diseases, defective apoptosis results in the extended cell survival and less proliferative activity. Chronic lymphoproliferative disorders include chronic lymphocytic leukemia (CLL), follicular lymphoma (FL), multiple myeloma (MM), and MZL [44].

The pathogenesis of these diseases is a multistep process involving stimuli arising from microenvironment that is important for disease propagation. Among certain elements of the microenvironment, some studies suggest that TLRs also play a crucial role in chronic lymphoid cancers. First, TLR-signaling initiation due to microbial infections such as HCV and *H. pylori* plays a role in B-cell lymphogenesis in MZL [46–50]. Second, a few genetic alterations are found in TLR genes that are associated with lymphoma pathogenesis [51,52]; genetic changes in TLR1, TLR6, and TLR10 are associated with NHL risk [51]. Moreover, SNPs in TLR2 and TLR4 genes have been associated with lymphoma susceptibility [52–54]. Lastly, for human myeloma cells, PAMPs play a role as growth and survival factors by stimulating TLRs in these cells [55–57]; for example, TLR9 agonists promote tumor growth by increasing myeloma cellular proliferation and survival [56,57].

In B-cell malignancies, TLR stimulation can induce various effects, and the involvement of TLRs in B-cell malignancies has been shown by knockdown studies of the MyD88 adaptor protein. In activated B-cell type (ABC) DLBCL cell lines, MyD88 knockdown results in a reduced proliferation rate, and this effect is dependent on the presence of oncogenic mutations [58]. In the MyD88 TIR domain, such oncogenic mutations are found in various types of lymphoma (Figure 2) including ABC DLBCL, gastric mucosa-associated lymphoid tissue (MALT) lymphoma [58], lymphoplasmacytic lymphomas [59], CLL, IgH-mutated CLL cases [60], and splenic MZL [61].

NF-κB is constitutively activated in normal or malignant B cells through BCR signaling, and this is an important pathway for evading cell death in various lymphoma subtypes. In mature BCLs, the presence of somatic mutations in NF-κB-related genes verifies the importance of NF-κB in lymphomas [62]. TLR-mediated activation of NF-κB provides a potential mechanism for enhancing proliferation and evading apoptosis. Likewise, in MM, TLR4 and TLR9 activation translocate NF-κB to nucleus, resulting in IL-6 production and enhanced cell growth [63]. Consistent with this, TLR2/6 and TLR2/1 ligation in CLL cells trigger NF-κB signaling and ultimately increases the survival rate of tumor cells [64].

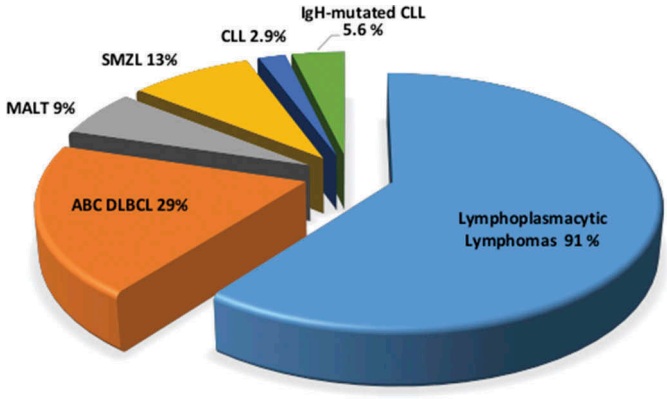

Figure 2. Prevalence of mutations in the MyD88-TIR domain in lymphoma. The extent of mutations and their correlation to various lymphoma types is presented. In lymphoblastic lymphoma, up to 91% of cases can be attributed to mutations in this domain, highlighting the importance of TLRs in these malignancies.

Various BCL subtypes are linked with bacterial or viral infections [65–68]. This leads to the speculation that chronic infections prompt the transformation of malignant B cells through long-term activation of proliferation pathways. Accumulation of genetic aberrations is favored by a prolonged proliferative state. Following the treatment of *H. pylori* infection, the regression and prolonged remission of gastric MALT lymphoma provides evidence to support this hypothesis [69,70]. Associations between infection and B-cell activation, maturation, differentiation, and TLR expression pattern have been reported for specific lymphoma subtypes originating from the germinal center at different phases of differentiation (Figure 3). For instance, the likely lymphomas that can originate with antigen encounter include mantle cell lymphoma (MCL, which is TLR9 positive), CLL (TLR7 and 9 positive), and MALT lymphomas (which are TLR4 positive) [66,71]. TLR7, TLR8, and/or TLR9 triggered by ssRNA or CpG agonists are observed in BL and DLBCL lymphomas [72,73]. MZL (TLR9 positive) and CLL (TLR7, 9 positive) originate in the differentiation phase of malignant memory B cells. Viruses like HCV, human immunodeficiency virus, and Epstein–Barr virus are associated with these lymphoma subtypes [65,67,68]. Moreover, TLRs have also been implicated in class-switching recombination and somatic mutations that may culminate in non-immunoglobulin-based somatic DNA aberrations, and facilitate the cancerous development of germinal center B cells [74–78].

In short, even though some evidence has been provided for the possible role of TLRs in lymphoma, further studies are still required for a better understanding of TLR involvement in the transformation of malignant cells due to chronic and prolonged infections or the induction of somatic mutation-prone cellular conditions.

5. Lymphoma treatment and TLRs

TLRs can be used in various ways to treat lymphoma. The following section will describe prominent approaches that have implications for lymphoma therapy.

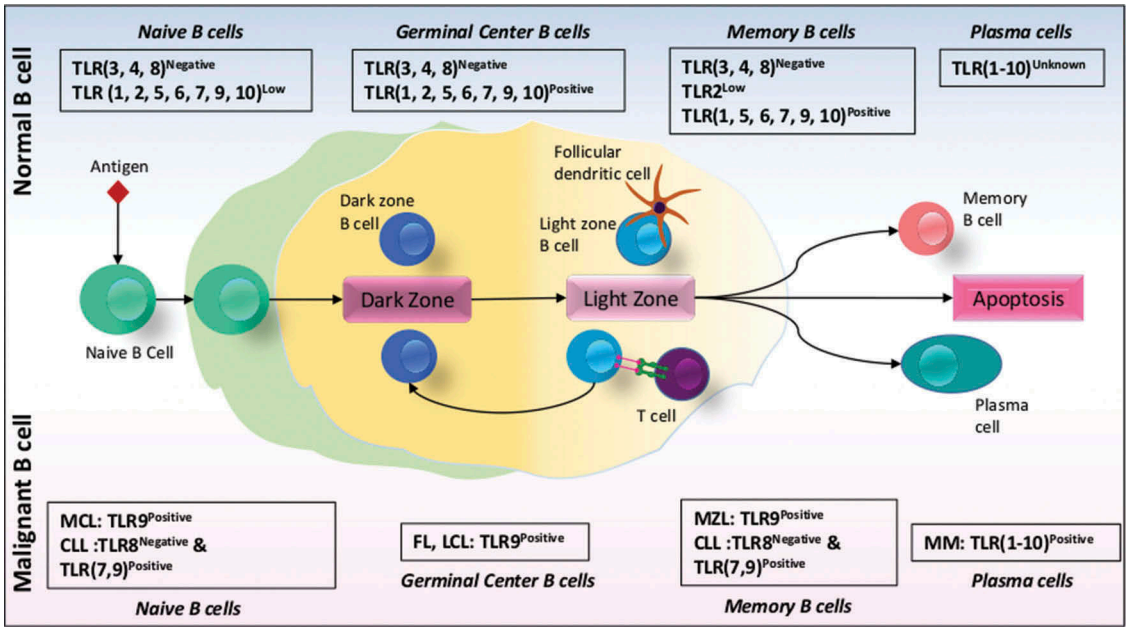

Figure 3. The comparative role of TLRs in normal and malignant B cells. TLR expression in normal and malignant B cells at different phases of B-cell differentiation, from antigen encounters to formation of memory B cells and plasma cells. This highlights the induction of specific types of lymphoma at various stages, and TLR expression in malignant and normal B cells.

5.1. TLR ligands for immune modulation

The contribution of TLRs toward lymphocytic malignancies by modulation of the immune system is well-documented, and the mechanism of how TLRs tune the immune system includes, but is not limited to, induction of costimulatory molecules, expression of pro- and anti-inflammatory molecules, modulation of T-cell functions, and the induction of regulatory cells.

TLR7 and TLR9 can induce the expression of cytokines, chemokines, and costimulatory molecules in CLL, BL, and acute myeloid leukemia that make tumor cells more immunogenic [72,79–82]. TLR7 activation makes CLL cells susceptible to targeting by cytotoxic T lymphocytes (CTL) [80,83]. TLR4 activation in primary MCL may worsen the disease by inducing the expression of IL-10 and vascular endothelial growth factor in tumor cells that resist CTL-mediated killing of target cells [84]. In acute lymphoblastic leukemia (ALL), TLR9 activation results in a skewed Th1 profile of T cells that helps in eradication of cancerous cells [83].

In the case of TLR2 stimulation, ALL cell lines may express costimulatory proteins [85]. Under normal conditions, B cells express IL-6/10 or IFN-γ in TLR-mediated pathways that result in immunosuppression and, in particular, upon TLR4/9 signaling, B cells express IL-10 that suppresses Th1 and Th17 cells. TLR2 promotes IL-10-producing Treg cells [86,87]. It has also been observed that patients with germinal center B-cell like (GCB)-DLBCL, FL, and classical HL have a higher number of Treg in the tumor microenvironment [88]. Moreover, the generation of Treg by B cells is MyD88-dependent, providing a link between TLR signaling and immune modulation [87].

In B-cell malignancies, the roles of TLRs in the tumor microenvironment and in immune response modulation have been supported with clear evidence. Various mechanisms may induce TLR expression and activation, depending upon the microenvironment, TLR, and lymphoma subtype [26]. TLR stimulation can favor the proliferation of malignant B cells by facilitating immune evasion via the induction of Treg cells and immunosuppressive cytokines [26].

5.2. Antitumor activity of TLR ligands

An amalgam of various experimental methods has been utilized to develop molecules that activate antitumor immunity, and the identification of TLRs as target molecules has led to the design of specific and potent immunostimulatory molecules. In the 1890s, William Coley found that toxins from dead gram-negative and gram-positive bacteria have antitumor effects [89,90], and it was later determined that LPS and bacterial DNA are responsible for this phenomenon. Currently, TLR agonists are being used as vaccine adjuvants and therapeutic drugs for the treatment of cancer and other diseases [91]. Especially, TLR9 agonist CpG-oligodeoxynucleotides (CpG-ODNs) have shown antitumor effects toward NHL, melanoma, glioblastoma, renal cell carcinoma, and cutaneous T-cell lymphoma [92] and are being tested against NHL in clinical trials [93]. One of the *in vitro* studies showed that CpG-ODNs can induce apoptotic cell death and inhibit B-cell proliferation in lymphoma, and in cerebral and systemic lymphoma; hence, they can reduce tumor growth [94]. These findings support the development of a TLR9-targeted therapy to combat primary NHL [94].

Cytokine production from TLR4 and TLR9 pathways stimulates the adaptive immunity response and activates NK and CTLs [95]. Imiquimod is the first successful drug targeting TLRs, acting on TLR7 to produce proinflammatory cytokines in a MyD88-dependent manner, leading to antitumor effects and antiviral immunity [96]. For treating NHL, the oligonucleotide sequence ISS1018 (Identifier: NCT00403052) in

combination with antigens is being used in clinical trials [97]. There is another oligonucleotide-based drug, agatolimod [98], being evaluated to combat MZL, cutaneous T-cell lymphoma, FL, and NHL, which is currently under a phase II clinical trial (Identifier: NCT00091208).

The use of TLR7 ligands improves the effects of cytotoxic drugs doxorubicin and etoposide [99], and these ligands show the same effect during fludarabine treatment, which is used for treating indolent NHL [100]. Furthermore, treating CLL cells *in vitro* with imidazoquinoline (S28690) activates the cells that make them vulnerable to CTLs [80].

In FL, the immunosuppressive effects of Treg were successfully inhibited by TLR1/2, TLR5, and TLR9 activation using their respective ligands Pam3CSK4, flagellin, and CpG-B. TLR ligands work in a synergetic manner to restore FL tumor-specific effector T cells by inhibiting Treg [101]. Moreover, in DLBCL patients, the anti-inflammatory effects of bromodomain and extra terminal domain-containing proteins inhibits normal B cells, leading to the early downregulation of BCR and TLR signaling pathways, including TLR10 and MyD88, which is helpful in treatment [102,103].

5.3. TLR ligand-conjugated vaccination and immunotherapy

Targeting crucial immunosuppressive activities using immunotherapeutic approaches has proven to be successful in enhancing tumor-specific T-cell activity; however, it is not clear whether this can work in tumor cells or not. Currently, appropriate immunotherapies using vaccination are lacking [104]. To improve vaccine design, various immune processes by which tumor cells influence the tumor microenvironment have been evaluated.

In cancer patients, tumor antigens initiate the humoral immune response and stimulate $CD8^+$ or $CD4^+$ T cells [105]. Thus far, a wide range of tumor antigen proteins and peptides have been identified that can be used to prepare cancer vaccines. Tested in a small number of patients, the first generation of these cancer vaccines showed beneficial results in clinical trials [106,107]. *In vivo* administration of protein- or peptide-based vaccines stimulates a weak immune response. B-cell lymphoma is exclusively derived from antigen presenting cells (APCs), which express few TLRs. Small, well-defined TLR agonists can be easily linked to peptides, and these conjugates can directly activate tumor-specific antigen-presenting DCs. To improve the efficacy of peptide-based vaccines for immunotherapy, single and supramolecular conjugate vaccines have been generated to induce an immune response [108,109], such as aluminum salts, non-toxic derivatives from Salmonella, and saponins (AS01, ISCOM, AS02, and QS-21). To date, the TLR ligands evaluated in clinical trials are imiquimod and resiquimod, prepared from ligands of TLR3, TLR4, and TLR7/8. Certain TLRs perform multiple functions, for instance, TLR3 signaling is involved in activating NK and AP cells and initiating tumor cell death. Therefore, utilizing agonists targeting TLR3 can be beneficial.

The ability of CpG motifs to activate normal human B cells led to the development of ODN 7909 [110] and currently, it is being tested as a vaccine adjuvant in clinical trials for the treatment of various cancers and NHL [93]. CpG has most frequently been used in mouse models; however, in humans the expression of TLR9 is confined to a small number of DCs; thus, this adjuvant molecule may not be suitable for clinical applications. Alternatively, the synthetic lipopeptide, tripalmitoyl-*S*-glycerylcysteinyl-seryl-serine, is being used for various treatment purposes [111]. Administering low doses of peptides conjugated with TLR ligands effectively induces $CD4^+$ and $CD8^+$ T-cell priming in tumor models of lymphoma, melanoma, and HPV16-induced tumors [112]. This observation yielded an optimized TLR2 ligand-based vaccine, suggesting that single peptide-TLR conjugates are effective for intradermal vaccine delivery [113].

Currently, many TLR ligands have been used as adjuvants in vaccines as a combination therapy against tumor malignancies. Advancements in the development of vaccines that combat different types of cancers, including lymphoma, have aided in understanding immune response mechanisms induced by vaccines [114]. A better understanding of these mechanisms will be crucial for improving the essential components and developing optimized and effective vaccines or immunotherapies.

5.3.1. Antigen peptide-based nanovaccine

For effective cancer treatment via vaccination, there is a dire need to develop a rational, targeted approach for vaccine delivery. The design of peptide-based vaccines for uninterrupted delivery to lymph nodes, where DCs induce CTLs, has been proposed [115]. To accomplish this, the use of nanoparticles as carrier molecules is a promising strategy for targeted vaccine delivery [116–118]. A small, biocompatible nanovaccine (α-AP-FNP) with a phospholipid monolayer shell has been developed for the directed delivery of antigen peptides to mature DCs. This small ~30 nm nanovaccine containing a fusion peptide is efficient in peptide loading, accumulating in lymph nodes, DC targeting, and enhanced antigen presentation [119]. A nanovaccine encapsulated with CpG-ODN that was altered with cholesterol (α-Ap-NP-CpG) has been generated [119]. α-Ap-NP-CpG has been tested in a mouse tumor model of lymphoma at 45 days after tumor inoculation that showed an improved survival [119]. Moreover, endosomal internalization of CpG allowed for efficient interaction with TLR9, and enhanced the antitumor effects of α-Ap-NP-CpG. The problem of tolerance caused by immature DCs (imDCs) can be solved using this approach and provides an attractive option for clinical applications [119].

5.3.2. TLR-mediated DC activation

DCs are bone marrow-derived cells with the ability to modulate and initiate the adaptive immune response. DCs consist of two major subsets: plasmacytoid DCs (pDCs) and conventional DCs also known as myeloid DCs (mDCs) [120]. DCs are mature APCs and they express multiple PRRs including TLRs; therefore, antitumor immune responses may largely depend on DCs. DC inactivation results in immune tolerance due to the inhibitory signals produced by tumor cells, thus promoting tumor growth [120,121]. Shifting the balance to DC-mediated

antitumor responses can be achieved by modulating the TLR-IFN signaling axis.

The vital element of DCs which is composed of receptors and involved in microbial recognition can be targeted for immunotherapy. Activation of antitumor immunity mediated by PAMPs is associated with the therapeutic effects induced by activation of DCs [122]. TLR-mediated activation of DCs, particularly by Imiquimod ligand for TLR7 and TLR8, can be antitumorigenic, imparting cytotoxicity and inducing tumor cell lysis [123,124]. Likewise, the antitumor activity of DCs is also mediated by activation of TLR5 [125], TLR9 and TLR3 by their respective ligands [120]. In the last decade, targeting DCs for immunotherapeutic cancer vaccines has been thoroughly investigated. However, the failure of this approach in clinical trials generated doubts regarding its efficacy. Regardless, extensive studies on DC immunobiology have led to the development of more efficient DC-based vaccines. In 1995, the first trial was conducted for an antigen-based DC vaccine against melanoma, and so far, over 300 clinical trials have been conducted indicating successful outcomes [126].

5.4. Genetic changes of TLRs in lymphoma

Functional polymorphisms in inflammatory genes such as TLRs may influence sensitivity to lymphoma. Some TLR alleles with functional relevance result in susceptibility to lymphoma, inflammation, and infectious diseases [51,52]. The first study of TLR mutations reported an Asp299Gly mutation in TLR4 that results in susceptibility to DLCL and MALT lymphoma [51,53,54], showing the association of TLR gene variants with specific lymphoma subtypes. TLR4 modulates B-cell activation at multiple stages, and TLR4-G allele-mediated signaling is weaker than normal TLR4 signaling, affecting NF-κB activation and inflammatory responses. The TLR2 mutation 16933 T > A is inversely associated with FL risk, whereas in patients with CLL, the TLR2-16933A allele was underrepresented [51,52]. TLR2 genetic changes shift homeostasis of the immune system after pathogen invasion and modulate the immunopathological effects. Another example of genetic changes in TLR is the TLR9-1486 T > C variant, which shows a strong association with childhood viral infection and a weak association with FL and CLL lymphoma [52] (Table 1). Moreover, TLR9 mutations have been linked to NHL risk: however, further studies are required [127,128].

In genetic aberrations, specifically 13q abnormalities, TLR9-mediated cell death has been reported in CLL cells after treatment with the TLR9 agonist CpG [129], which may also induce overexpression of FAS and death receptor 5. However, it will also initiate other pathways like mitochondrial death pathways [130]. Furthermore, CpG oligonucleotides can be used synergistically with other lymphoma treatments. In CLL, pretreating lymphoma cells with CpG facilitates the uptake of toxins by overexpression of CD25, which in turn improves the effect of IL-2R toxins on cells [131]. Moreover, overexpression of CD20 in TLR9 signaling facilitates rituximab treatment, which targets CD20 [132,133].

5.5. Negative regulation of TLRs

When TLRs activate the inflammatory response, regulatory mechanisms also commence to avoid self-damage [134]. Among these mechanisms, suppressor of cytokine signaling (SOCS) proteins are crucial for maintaining a balance in TLR-mediated inflammatory responses and are known as inducible feedback inhibitors of cytokine receptors. SOCS proteins are directly triggered by TLR activation, and they prevent over-activation of the inflammatory response without affecting TLR signaling [135]. In certain types of lymphoma, DNA hypermethylation causes reduced expression, mutation, or deletion of the SOCS1 gene. Reduced expression of SOCS1 promotes cell proliferation by enhancing JAK2 activity and can trigger the B-cell lymphoma-linked oncogenic pathway [136]. Therefore, targeting the genes that negatively regulate TLR signaling can be another potential therapeutic approach for the treatment of lymphoma.

6. Conclusion

Knowledge regarding the influence of TLRs on lymphoma cells has improved tremendously over the last few years, leading to the increased use of TLR ligands as a mean of antitumor therapy. The dual role of TLRs in lymphoma is well appreciated, and TLR serves as a double-edged sword in various inflammatory conditions and cancers. In lymphoproliferative malignancies, TLRs are involved in the transformation of malignant cells as well as tumor progression and regression. A strong correlation exists between severe infections and lymphoma development, indicating that malignant transformation is directly linked to TLRs. Therefore, modulating TLRs can be utilized in lymphoma treatment to benefit patients. Moreover, the discovery of novel TLR ligand-based therapeutics will improve the efficacy and specificity of treatment options for future clinical trials. Further studies are required to explore other targets in TLR pathways and pathways being influenced by TLRs to obtain a better understanding of disease pathology and ways to modulate the immune system.

7. Expert opinion

Any abnormality that arises in the body is a failure of the immune system to respond properly. Either underactivation or overactivation of various immune system components can lead to various diseases, which can either be locally oriented or influence other organs. There has been enormous progress in the development of lymphoma treatment options, which has drastically improved the survival rate of the lymphoma patients. However, the number of deaths associated with lymphoma remains significant. There is an urgent need to develop patient specific, highly active, low-dose treatment regimens with fewer side effects to effectively treat these neoplasias. TLRs are vital components of immune cells that can significantly modulate the immune system under various conditions [137]. The potential use of TLR-related therapies for various diseases is gaining momentum, numerous attempts

have made to utilize TLRs for disease treatment, and very promising results have been reported in various studies.

TLRs have a dual role in inflammation and carcinogenesis: their activation can either prevent disease progression or worsen the pathology. This dual nature of TLRs demands the careful use of their activating or inhibiting ligands. Furthermore, the modulation of intracellular mediator proteins, for instance, IRAK4 inhibitors (ND-2158 and ND-2110), has been successfully utilized to target B-cell lymphomas and other autoimmune diseases [138]. Such types of intracellular targets that are very specific, selective, and unique are ideal targets.

MyD88 is the unique and vital adaptor protein of all TLRs, excluding TLR3. Because it is an adaptor protein, it is difficult to target through conventional means. However, a crystal structure that highlights the structural assembly of MyD88/IRAKs, termed as myddosome, has been reported and it may be a good drug target [139]. This hierarchal assembly could provide multiple options for disrupting this complex and blocking its signaling.

The structure–activity relationship of TLRs is of great interest to help in understanding their signaling. For instance, two mutations in the TLR4 ectodomain, D299G and T399I, can ablate TLR4 signaling, whereas the influence of these two mutations on structure is minimal. Similarly, mutated MyD88, $MyD88^{L265P}$, has been frequently identified in different lymphomas, and is positively correlated with disease occurrence and pathogenesis [140]. Such polymorphisms either inhibit signaling pathways or overactivate them. $MyD88^{L256P}$ continuously activates TLR signaling, contributing to lymphoma; therefore, a ligand that can target MyD88 can limit TLR signaling in various diseases and help to cure lymphomas.

TLR activation also promotes the expression of negative regulators that precisely control the inflammatory intensity and limit the overactivation of other complementary pathways. These negative regulators of various types act in various manners, from inhibiting gene expression to inhibiting protein function. Numerous proteins can be exploited that bridge TLR pathways and other pathways such as the TNF-α pathway [141]. Dual-specificity phosphatase (DUSP) 4 is one such protein and hypermethylation impedes its transcription. DUSP4 could potentially be a tumor suppressor protein in ABC-DLBCL, GCB-DLBCL, or mediastinal B-cell–like lymphomas. Therefore, it is necessary to find such targets through expression profiling and mass-spectrometry techniques.

In cancer, recurrence has several causes and is a major problem. To completely eradicate cancer cells, it is imperative to treat patients with a combination of drugs. Combinatorial therapy has a higher chance to suppress the disease and prevent its recurrence. In combinatorial therapies, the addition of TLR ligands to modulate the immune system could be beneficial. By this method, the side effects of cytotoxic drugs could also be alleviated. This strategy has already been tested in DLBCL and MCL with antibodies; however, other modes of inhibition could be exploited with TLR ligands. Moreover, personalized medicine has a great potential for cancer treatment, and various drugs tailored for various persons/cancers can reduce the side-effects and may effectively treat those neoplasms.

The side effects of cytotoxic drugs are always a hurdle for effective lymphoma control. The drugs used in chemotherapy are inherently cytotoxic, killing the normal cells and aggravating patient health. Immune modulation is a viable option in this case, and it can be safely achieved by utilizing various TLR ligands. TLRs can effectively modulate the immune system with fewer side effects and higher specificity than cytotoxic therapy. Moreover, engaging the immune system to combat self-altered cells could be the key to unlocking the potential of the immune system in cancer therapy. TLR expression patterns are variable in different immune cells, necessitating the usage of their ligands with care. Moreover, their expression profile in normal cells should be delineated to gain further understanding of their expression in various types of lymphomas.

Conformational ensemble-based pharmacophores should be devised to target specific proteins because proteins are dynamic in nature and the true picture of protein dynamics cannot be identified though crystallographic techniques. For this, atomic molecular dynamics simulations should be performed to provide a better picture of protein dynamics and improve pharmacophore properties. Antibody-mediated TLR activation may also be sought out to optimize TLR activation. Antibody treatment may disrupt serum protein balances; however, it is safer than cytotoxic therapy and can be modified for long-lasting action.

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Declaration of interest

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