The role of toll-like receptor in cancer progression: A viable therapeutic target?

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Abstract The toll-like receptor (TLR) household consists of critical receptors accountable for pattern recognition in innate immunity, making them the core proteins concerned in pathogen detection and eliciting immune responses. The most studied member of this family, TLR4, has been the core of interest concerning its contributory position in many inflammatory ailments along with sepsis shock and asthma. Notably, mounting pieces of proof have proved that this receptor is aberrantly expressed on the tumor cells and the tumor microenvironment in a vast range of most cancers sorts and it is highly related with the initiation of tumorigenesis as nicely as tumor progression and drug resistance. Cancer remedies the use of TLR4 inhibitors has currently drawn scientists' attention, and the promising outcomes of such research may additionally pave the way for more investigation in the foreseeable future. This evaluation will introduce the key proteins of the TLR4 pathway and how they have interaction with foremost boom elements in the tumor microenvironment. Moreover, we will talk about the many factors of tumor progression affected by using the activation of this receptor and furnish an overview of the current therapeutic processes the use of a range of TLR4 antagonists.

Keywords Cancer, Immune escape, Inflammation, Metastasis, Targeted therapy, Toll-like receptor 4 (TLR4)

1. Introduction

Toll-like receptors (TLRs) are a family of pattern-recognition receptors mostly expressed on the surface of cells involved in innate immunity; they can also be expressed and translocate into endosomes. Toll-like receptors (TLRs) play a key role in the activation of innate immunity due to their ability to recognize highly conserved molecules expressed by pathogens. Alongside pathogens associated molecular patterns (PAMPs) [1]. TLRs can also detect endogenous ligands (alarmins, also called danger-associated molecular patterns or DAMPs). TLR is a trans-membrane protein of type I that has an extracellular domain and an intracellular domain. Alarmins are excreted by cells in response to tissue injury or cell death, but their overproduction has been linked to autoimmune diseases and cancer [2]. Cell death and chronic inflammation are key features of tumorigenesis, resulting in increased alarmin production in many types of cancer, including breast, colon, pancreatic, melanoma, and glioblastoma. There are currently 11 mammalian TLRs known. TLR4 is one of the most extensively researched TLRs. The majority of

studies on Toll-like receptors (TLRs) have concentrated on their expression pattern and function in immune system cells. TLR expression and function in cancer cells, as well as the links between TLRs and oncogenesis and tumour progression, have recently sparked considerable interest [3]. The first member of this family was discovered in Drosophila, and based on its homology. The first mammalian TLR was TLR4 identified in human monocytes in 1997 by Medzhitov et al. (1997). TLRs' ability to detect foreign materials, known scientifically as pathogen-associated molecular patterns (PAMPs), allows them to play an important role in the activation of innate and then adaptive immune responses by initiating a downstream signaling cascade that results in the release of various types of cytokines and chemokines, as well as immune cell maturation. TLR4 has been the focus of scientific attention in recent years as one of the most important members of the TLR family [4]. This receptor is best known for its ability to detect the main PAMP, lipopolysaccharide (LPS) from gram negative bacteria. TLRs in general, and TLR4 in particular, are implicated in many cancer types in the current literature. However, data linking TLRs to breast cancer are very limited, and it is unclear whether the effect of TLR4 on breast tumorigenesis is due to cancer cell intrinsic or immune-mediated effects. TLR-induced pro-inflammatory reactions have long been the subject of extensive research in the field due to the possibility of using them for cancer immunotherapy [5]. In this review, we will first discuss the dual role of TLR ligands in cancer progression and therapy, as well as the rationale for using these agents to treat cancer.
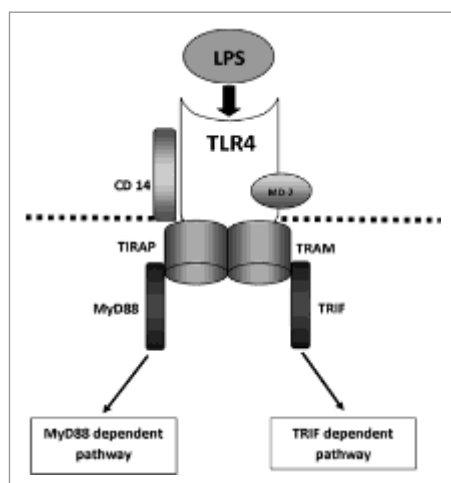
Overview of TLRs

TLRs were first linked to immune responses when it was discovered that mutations in the Drosophila toll receptor resulted in a high susceptibility to fungal infections and a defective production of antifungal peptides. TLR4 and MyD88 have been found to be overexpressed in breast cancer, implying a role for the TLR4 signaling pathway in the tumour microenvironment. TLRs send signals to the nucleus via adaptor proteins, where they regulate the innate and adaptive immune responses. Since Deidier discovered that patients infected with syphilis developed very few malignant tumours nearly 300 years ago, it has been known that bacterial infection can cause cancer remission by activating the immune system [6,7]. TLR4 is expressed not only on tumour cells but also on stromal and immune cells, which play an important role in antitumor immunity in the tumour microenvironment. TLRs are crucial in tissue repair and regeneration. TLR signaling pathways activation can result in increased transcription of genes encoding type I interferons (INF), various pro-inflammatory cytokines such as TNF-, IL-1, and IL-6, as well as anti-inflammatory molecules such as IL-10, COX-2, and prostaglandin E2. TLR4 activation in the tumour microenvironment has been shown to boost antitumor immunity, including dendritic cell (DC) maturation and antigen presentation. It should be noted, however, that the type and level of cytokines induced are primarily determined by the type of TLR-activated cells [8,66]. TLR4 activation in macrophages, for example, results in the secretion of pro-inflammatory cytokines such as TNF- and IL-1ß, whereas TLR4 activation in DCs primarily

induces the secretion of IL-12 [65]. Furthermore, the type of activated TLR can influence the type of cytokines that are predominantly secreted as a result of activation. Ligation of 9 out of 10 human TLR homolog's with PAMP/DAMP agonists can activate a common signaling pathway mediated by the interaction of their TIR signaling domains with the adaptor protein myeloid differentiation factor 88 (MyD88), resulting in the initiation of a complex cascading series of interactions with downstream cytoplasmic proteins. [9,10]

Types of TLRs

TLR family members have been identified in humans 10 times and in mice 13 times. There are 11 mammalian TLRs that have been identified. TLR4 is one of the most extensively researched TLRs. TLR1, 2, 4, 5, 6, and 10 are primarily expressed on the plasma membrane, from which they migrate to phagosomes after ligation with their respective agonists [11]. These can mostly recognise bacterial organisms' outer components, such as the lipoprotein of Gram-positive bacteria (TLR1, 2, 6, and 10), the lipopolysaccharide (LPS) of Gram-negative bacteria (TLR4), and the flagellin of bacterial flagella (TLR5). TLR3, 7, 8, and 9, on the other hand, are found on the endosomal compartment and are mostly capable of alerting the host to intracellular infections by recognising bacterial or viral nucleic acids [12]. TLR2 recognises a variety of bacterial components, including peptidoglycan, lipopeptides, and lipoproteins from gram-positive bacteria and mycoplasma. TLR3 recognises them and causes T cells to activate. TLRs are thought to be an important link between the adaptive and innate immune systems. INFs are the most common cytokines secreted in response to TLR3, 7, 8, and 9, whereas TNF- and IL-12 are commonly secreted in response to TLR2 and 4 [13].

| TLRs	Ligands
TLR1	Triacyl lipopeptides
TLR2	Lipoprotein/lipopeptides, peptidoglycan, lipoteichoic acid, etc
TLR3	Double-stranded RNA
TLR4	LPS, HSP60, etc, commensal bacteria
TLR5	Flagellin
TLR6	Diacyl lipopeptides, Zymosan, Peptidoglycan/Lipoteichoic acid
TLR7	Imidazoquinoline, Synthetic Compounds (the immune response modifiers)
TLR8	Single-stranded RNA
TLR9	CpG-DNA, Bacterial DNA
TLR10	Unknown

Types of TLRs
TLR Signaling

Mammalian TLRs are made up of an extracellular domain with leucine-rich repeats for ligand binding, a transmembrane region, and a cytoplasmic Toll/interleukin-1 receptor (TIR) domain for intracellular signaling. TLRs localise in different subcellular compartments depending on the component with which they interact [14]. TLRs that recognise lipid and protein ligands (i.e., TLR1, TLR2, TLR4, TLR5, and TLR6) are thus expressed on the plasma membrane, whereas TLRs that detect nucleic acids (i.e., TLR3, TLR, and TLR9) are expressed in endolysosomes. TLR-induced intracellular signaling is archived by one of four adaptor proteins: -

1. myeloid differentiation factor 88 (MYD88),
2. TIR-domain-containing adaptor inducing IFNβ (TRIF),
3. TIR domain-containing adaptor protein (TIRAP)
4. TRIF-related adaptor molecule (TRAM)

TLRs (except TLR3) and IL-1 receptor family members communicate via MYD88. TLR3 communicates via TRIF, whereas TLR4 communicates via both the MYD88 and TRIF pathways [15,16]. TLR binding activates nuclear factor B (NFB), mitogen-activated protein kinases (MAPKs) such as c-JUN N-terminal kinases (JNKs), p38 and extracellular signal-regulated kinases (ERKs), and IFN-regulatory factors 3, 5, and 7 (IRF3, IRF5, and IRF7) signaling pathways. Both innate and adaptive immune responses rely on these signals [17,67].
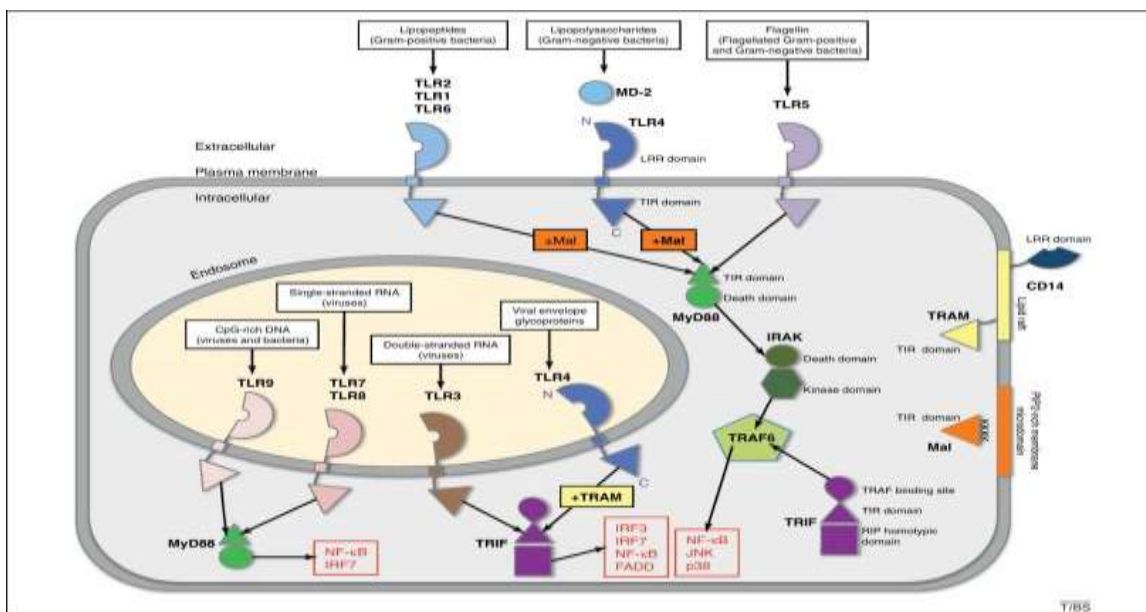
TLR4 Signaling

TLR4 is the only TLR known to date that can signal via both MYD88-dependent and MYD88-independent (TRIFdependent) pathways. The MYD88-dependent signaling pathway was shown to be responsible for pro-inflammatory cytokine expression in studies using MYD88-deficient macrophages, whereas the MYD88-independent pathway appears to mediate the induction of Type I IFNs and IFN-inducible genes [18,19]. MYD88-dependent signaling pathway Upon LPS stimulation, the TLR4 signaling complex's MYD88 subunit recruits and activates a death domain (DD)-containing kinase, IL-1 receptor-associated kinase 4. (IRAK-4). IRAK-4 is an IRAK protein that contains both death and kinase domains. MYD88 also contains a DD that, through homotypic interactions, can recruit other DD-containing molecules [20,68].
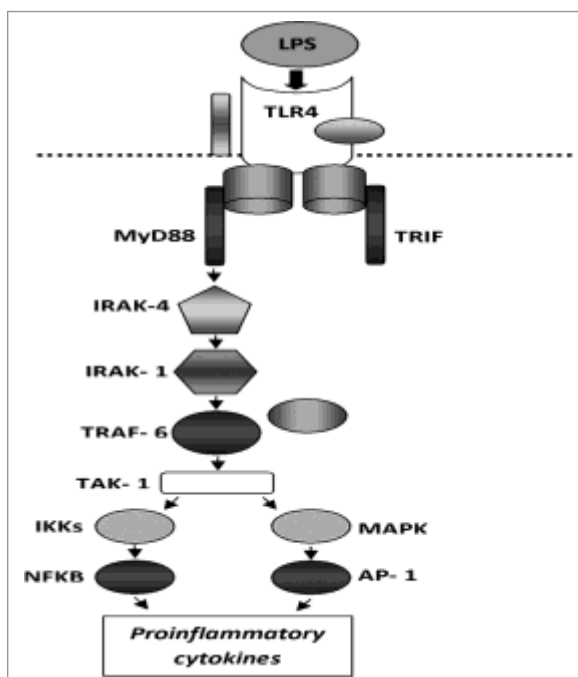
TLR4 Signaling

IRAK-4, like MYD88, plays an important role in the cytokine response to LPS stimulation. When stimulated with LPS, macrophages lacking IRAK-4 produce significantly less pro-inflammatory cytokines. In fact, mice lacking IRAK-4 are resistant to LPS-induced septic shock [21]. According to biochemical evidence, IRAK-4 activation is responsible for the subsequent recruitment, activation, and degradation of IRAK-1. Interestingly, IRAK-1-deficient mice produce some cytokines in response to LPS stimulation, implying that other molecules are involved in IRAK-4 downstream signaling [22]. Recent evidence suggests that IRAK-2 is involved in this process. The activation of TNF receptor-associated factor 6 is the next step after IRAK-1 activation (TRAF6). TRAF6 forms a complex with ubiquitin-conjugating enzyme 13 (UBC13) and ubiquitin-conjugating enzyme E2 variant 1 isoform A (UEV1A), activating TGFβ-activated kinase 1(TAK1) [23]. TAK1 then stimulates the NFκB and MAPK signaling pathways. TAK1 specifically activates the inhibitor of kappa-B (IκB) kinase (IKK), which is composed of the IKKα, IKKβ, and IKKγ subunits, to phosphorylate IκB proteins. Phosphorylation of IκB results in its degradation, which allows for the nuclear translocation of NFκB, which regulates the expression of pro-inflammatory cytokines and other immune-related genes [24]. TLR4 activation activates the transcription factor activator protein-1 (AP-1) signaling pathway, which controls the expression of pro-inflammatory cytokines. Another effector activated by the TRIF pathway is IRF3. Evidence suggests that IRF3 is not activated by RIPK1. TRAF3 has been linked to this process and the subsequent induction of type I IFNs [25]. TRAF3 can interact with TRAF family member-associated NFκB activator (TANK), TANK binding kinase 1 (TBK1), and IKKi to mediate downstream signaling. TBK1 and IKKi are required for IRF3 dimerization and translocation. IFN and IFN-inducible gene induction is critical for antiviral and antibacterial responses.

TLR4 Signaling
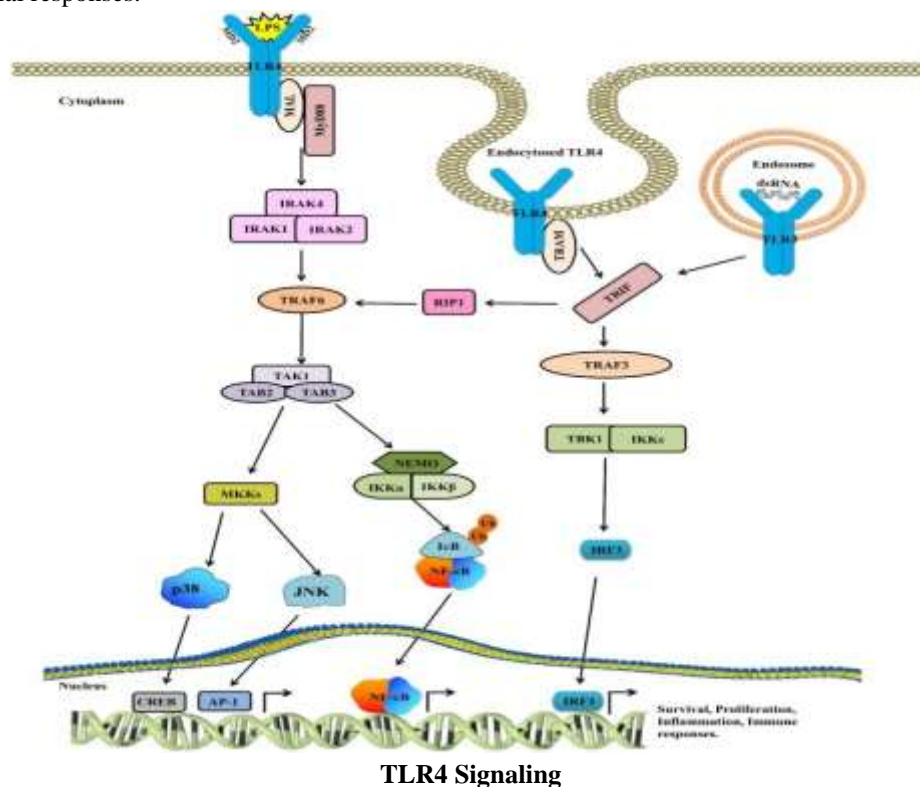
## The Relation Between TLR4 and T Cells in Tumor Microenvironment

CD4+ T cells can be divided into Th1, Th2, T helper 17 (Th17), regulatory T (Treg), and T follicular helper cells, all of which play a dynamic role in immune responses to infectious diseases as well as cancer. TLR4 agonists such as glucopyranosyl lipid A-stable emulsion (GLA-SE) and LPS can boost the Th1 response. According to research, synthetic GLA can definitely upregulate the CD4+ T cell response by increasing IFN-γ and TNF production [26,69]. Consistently, recent studies confirmed the existence of CD4+ CTLs, newly discovered members with the function of

killing autologous B cells presenting MHC II complex, implying the pivotal role of TLR4 in activating CD4+CTLs [27]. This newly defined CD4+ T cell function is dependent on CD40L engagement of CD40 in target cells rather than a previously discovered specific CTL mechanism. CD4 CTL expressed some markers associated with CD8 CTL cytotoxic functions, such as natural killer group 2 (NKG2A) and NKG2D. Given the importance of CD4 CTLs in the control of HIV, malaria, and other infections, it is intriguing to speculate on the activity of CD4 CTLs in the tumour environment following TLR4 agonist adjuvant [28]. Nonetheless, a review found that CD4 CTL affect both protective and pathogenic immunity, implying that the function of CD4 CTL on tumour cells in the tumour microenvironment should be investigated further.

Expression of TLRs in Different Types of Cancer

TLRs are expressed by antigen-presenting cells (such as dendritic cells and macrophages), fibroblasts, and epithelial cells, and their primary function is to protect the host from microbial infection [29]. However, functional TLRs are found on cancer cells, and their expression is frequently linked to disease prognosis. The same receptor can be associated with either a good or a bad prognosis (as in TLR9), or it can be associated with a bad outcome in general (like TLR4) [30]. This makes studying TLRs as a whole in the context of oncogenesis and cancer progression difficult, and suggests that studying single receptors in specific types of cancer may be a better approach. Different cell populations (for example, cancer stem cells, cancer cells, tumor-infiltrating lymphocytes, tumor associated fibroblasts, etc.) may express different TLRs and, as a result, respond differently to TLR stimulation [31]. TLR expression in normal, pre-malignant, and malignant esophageal and oral cavity epithelium is discussed in a recent review. It focuses on TLR2, 4, and 5, which are normally expressed on cell membranes but increase in expression and become more cytoplasmic during dysplasia and cancer. It is concluded that changes in TLR locations and constitutive activation can result in chronic inflammation and tumour progression rather than transient inflammation and tumour eradication [32]. TLR expression and the direct pro- and anti-tumor effects of TLR ligands on cancer cells have recently been studied. Glioblastoma stem cells have very low TLR4 expression compared to non-stem cells and do not respond to TLR4 stimulation, allowing them to survive in the face of immune signaling. The authors demonstrate a direct relationship between TLR4 signaling and stemness, and they propose a treatment strategy based on TLR4 re-expression. Despite low TLR4 expression, glioblastoma stem cells express high levels of TLR2, and stimulation of TLR2 by high-mobility group box 1 (HMGB1) increased stemness markers in those cells [33].
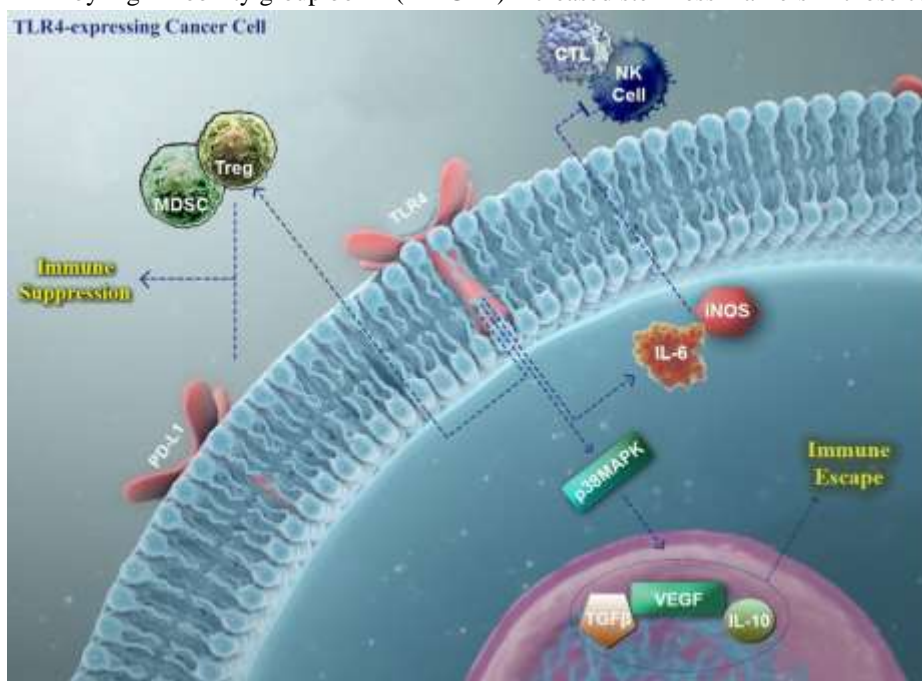
Expression of TLRs in Different Types of Cancer

TLR4 and Breast Cancer

The relationship between TLR4 and breast cancer has been studied from various perspectives, yielding several intriguing results. At the cellular level, after systemic administration of LPS, breast cancer cells exhibit increased migration, invasion, and angiogenetic behaviour at secondary sites [34]. The intraperitoneal injection of LPS into BALB/c mice with metastatic breast adenocarcinomas derived from 4T1 cells promoted angiogenesis both in vivo and in vitro. Furthermore, activation of TLR4 on metastatic breast cancer cells has been shown to regulate the expression of integrin αvβ3, TPM1, and maspin, and thus to promote cancer cell αvβ3-mediated adhesion and invasiveness [35]. Finally, TLR4 signaling appears to boost miR-21 expression in breast cancer cells by activating NFκB. As a result of TLR4-induced NFκB activation, breast cancer cells may develop a high metastatic potential. TLR4 is expressed by 20% of mononuclear inflammatory cells in the breast tumour micro-environment, and TLR3, TLR4, and TLR9 expression levels have been proposed as indicators of tumour aggressiveness [36,70]. TLR4 was found to be expressed at higher levels than any other TLR in the human breast cancer cell line MDA-MB-231. TLR4 knockdown resulted in a significant decrease in cell viability as well as IL-6 and IL-8 secretion. TLR4 knockdown inhibits the survival and proliferation of breast cancer cells, according to this study [37].

Anti-tumor Role of TLR Stimulation

Antitumor properties of bacteria and their products have long been known. Deidier's initial work was followed by Coley's development of a sarcoma treatment using a mixture of bacterial toxins. Coley's findings were not widely accepted by medical society due to inconsistencies and were not followed for a long time; however, he is now often referred to as the "Father of Immunology." Many years later, lipopolysaccharide (LPS), an outer membrane component of Gram-negative bacteria, was identified as an active fraction of Coley's toxin, implying the involvement of TLR4 activation [38,39]. Because of their systemic toxicity, LPS and other bacterial products must be administered locally, frequently via intra-tumoral injection. An attenuated strain of Clostridium novyi was recently shown to effectively reduce tumour size not only in a rat model but also in dogs with spontaneous solid tumours and one sarcoma patient. Clostridium novyi spores germinate only in hypoxic regions of cancerous tissue and induce an immune response, most likely through TLR activation [40]. Bacillus Calmette-Guérin (BCG), an attenuated strain of Mycobacterium bovis developed as a tuberculosis vaccine, has been used as a treatment for bladder cancer for over 40 years. The precise mechanism of BCG action is unknown, but its anti-cancer effect is caused by both the direct effect of BCG infection on cancer cells and the immune response to it. BCG, a TLR2/4 ligand, is one of three TLR ligands approved by the FDA [41]. TLR4 ligand monophosphoryl lipid A (MPLA) and TLR7 agonist imiquimod are the others. Although TLR ligands can be effective as monotherapy, they are typically used in combination therapy, often acting as vaccine adjuvants. Their efficacy as immunotherapeutic agents is primarily dependent on the induction of T-cell immunity—antigen uptake, processing and presentation, dendritic cell maturation, and T cell activation [42]. PAMP/DAMP binding to TLR on immature antigenpresenting cells (APCs) causes them to mature into professional APCs capable of presenting antigens (e.g., bacterial or cancer) on major histocompatibility complex I. (MHC I) [43,44].

Role of TLR Adaptor Proteins in Cancer

Because TLRs bind to cell membranes, TLR signaling is transmitted through adaptor proteins such as myeloid differentiation primary response-88 (MyD88) and TIR-domain-containing adapter-inducing interferon-β (TRIF).[44] TNF-α, interleukin-1 beta (IL-1β), interleukin-6 (IL-6), interferon gamma-induced protein 10 (IP-10), and IFN-γ are all induced by MyD88 and TRIF signaling via the transcriptional factors NF-κB, activator protein 1 (AP-1), and interferon regulatory factor 3. (IRF-3). Furthermore, MyD88 activation can trigger signaling cascades involving c-Jun N-terminal kinase (JNK) or extracellular signal-regulated kinase (ERK), leading to cell survival and proliferation [45]. MyD88 can also communicate with TLRs via interleukin (IL)-1 receptor families. Except for TLR3, all TLRs signal through MyD88, whereas TLR3 and some TLR4 signal through TRIF. Although MyD88 can interact directly with TLRs, it has been shown that an additional protein called TIR-domain containing adaptor

protein (TIRAP) facilitates MyD88 interaction with TLR2 and TLR4 [46]. To associate with TRIF, TLR4 requires the presence of another adaptor, TRIF-related adaptor molecule (TRAM). Mice lacking MyD88 were created in 1998 and have since been used to demonstrate the critical role of MyD88 in bacterial or parasite resistance. TLR and MyD88 signaling is involved in protective inflammation responses that regulate gut bacterial numbers and intestinal epithelial cell homeostasis [47,48]. However, the role of MyD88 in the development of colon cancer is more complicated. MyD88 was discovered to be a synthetic lethality target in colon cancer; it acts as a link between inflammatory signaling pathways from TLRs and oncogenic signaling from Ras. Inhibiting MyD88 increased the sensitivity of colon cancer cell lines to genotoxic agents in vitro and in vivo, reducing tumour growth and increasing apoptosis [49,50]. The most aggressive form of diffuse large B-cell lymphoma (DLBCL) is linked to a gain-of-function mutation in MyD88 (L265P). This mutant form of MyD88 promotes cell survival by increasing NF-κB signaling and activation of signal transducer and activator of transcription 3 (STAT3) [51].

Immune Escape and Survival

TLR4 is expressed in both immune and cancer cells, and activation by either endogenous or exogenous stimuli results in the overexpression of a wide range of cytokines depending on the type of stimulated cells. While TLR4 activation in immune cells results in an immune response against infectious agents, activation in tumour cells results in the opposite reaction, leading to immune-suppression and, eventually, tumour progression [52,53]. In fact, TLR overexpression in tumour cells is a mechanism by which these cells manipulate inflammatory pathways in order to proliferate indefinitely. TLR4 signaling may activate the p38 MAPK pathway, thereby increasing the activation of immunosuppressive cytokines like IL10, TGF-β, and VEGF [54]. In turn, these proteins influence immune cells and aid cancer cells in evading immune detection. TLR4 activation has been shown to promote the production of immunosuppressive cytokines TGF-β, VEGF, and pro-angiogenic chemokine IL8 by lung cancer cells, as well as immune escape and apoptosis resistance [55].

Therapeutic Targeting of the TLR4 Pathway

Given the importance of the TLR4 pathway in cancer progression, it has long been assumed that inhibiting it could slow the growth and invasion of TLR4 positive tumours. So far, industrial efforts have concentrated on developing molecules that selectively and specifically inhibit receptors or inhibit their interaction with downstream adapters [56,57]. These efforts have resulted in the creation of versatile monoclonal antibodies, LPS analogues, small molecule inhibitors, and functional small interfering RNAs (siRNAs). Eritoran (E5564) is a lipid structural analogue. A portion of LPS was created to treat severe sepsis [58]. However, some studies have found that it has an inhibitory effect on cancer cells. Kuo et al. (2016) found that giving Eritoran intracolonic, intragastric, or intravenous could reduce tumour burden and increase apoptosis in murine models of colorectal carcinoma [59]. Furthermore, it was demonstrated that by altering the tumour microenvironment, this inhibitor not only reduced tumour volume but also decreased tumour vasculature development and pulmonary recruitment of MDSCs in lung cancer patients [60]. TLR4 is highly expressed in immune system cells such as monocytes (e.g., DCs and macrophages), lymphocytes, and splenocytes, but it is also expressed at lower levels in epithelial and endothelial cells, as well as cancer cells [61]. TLR4 can be activated by natural ligands other than bacterial LPS, such as respiratory syncytial virus fusion protein and glucuronoxylomannan. Furthermore, it has been demonstrated that after activation by a diverse range of endogenous molecules (DAMPS), TLR4 (and TLR2) can promote sterile inflammation, i.e. inflammation caused by tissue damage and injury rather than bacterial or viral infections [62]. These molecular danger signals, which include heat shock proteins (HSPs), extracellular matrix degradation products, high mobility group protein B1 (HMGB-1), β-defensin, surfactant protein A, and minimally modified LDL, are frequently released or exposed by dying or stressed cells and are also significantly expressed by cancer cells dying as a result of radiotherapy and/or chemotherapy. The association of these molecules with the TLR4 expressed by immune cells is thought to contribute to the success of the aforementioned anticancer therapeutic strategies [63,64].

Conclusions

TLR4 is important in innate immunity because its activation by LPS is required for the host's defense against gram-negative bacteria. On the other hand, its overexpression within tumour cells and the microenvironment may contribute to cancer progression. TLR4 is activated by a variety of endogenous and exogenous molecular, bacterial, and viral ligands. The potent pro-inflammatory reactions that result provide a promising platform for cancer immunotherapy. TLR4 has been shown to play an important role in the presentation of antigens from cancer cells that have succumbed to chemotherapy or radiotherapy. Furthermore, TLR4 polymorphisms may influence an individual's susceptibility to breast cancer development and/or recurrence. Finally, it has been demonstrated that targeting TLR4 in breast cancer cells reduces their metastatic potential. Chronic inflammation caused by the TLR4 pathway contributes to tumorigenesis in a variety of cancers. In fact, activating the NFκB transcription factor and its versatile signaling crosstalk with other cancer promoting pathways causes immune suppression, cancer cell survival, metastasis, and drug resistance, at least in part.

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