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REVIEW

Toll-like receptors expressed in tumor cells: targets for therapy

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Abstract Toll-like receptors (TLRs), mainly expressing in human immune related cells and epithelial cells, play an essential role in the host defense against microbes by recognizing conserved bacterial molecules. Recently, the expression or up-regulation of TLRs has been detected in many tumor cell lines or tumors, especially epithelial derived cancers. Although the TLR profile varies on different tumor cells, the current evidences indicate that the expression of TLRs is functionally associated with tumor progression. TLR expression may promote malignant transformation of epithelial cells. Engagement of TLRs increases tumor growth and tumor immune escape, and induces apoptosis resistance and chemoresistance in some tumor cells. These findings demonstrate that TLR is a promising target for the development of anticancer drugs and make TLR agonists or antagonists the potential agents for tumor therapy.

Keywords Toll-like receptors · Tumor · Therapy · Target · Agonist

Abbreviations

BCGCWS	Bacillus Calmette-Guerin cell wall skeleton
CLL	Chronic lymphocytic leukemia
CpG	Deoxycytidyl-phosphate-deoxyguanosine
DC	Dendritic cells
HMGB1	High-mobility-group box 1
iNOS	Inducible nitric oxide synthase
IRAK	IL-1R-associated kinase
IRF-3	IFN regulatory factor 3
Lm	Listeria monocytogenes
LPS	Lipopolysaccharide
MyD88	Myeloid differentiation primary-response protein 88
PAMPs	Pathogen-associated molecular patterns
Poly(I:C)	Polyinosine-polycytidylic acid
TIR	Toll/interleukin-1 receptor
TLRs	Toll-like receptors
TRAM	TRIF-related adaptor molecule
TRAF6	Tumor necrosis factor receptor-associated factor-6
TRIF	TIR-domain-containing adaptor inducing IFN-β

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Introduction

Toll-like receptors (TLRs), the mammalian homologues of the Drosophila Toll proteins, play a crucial role in the host defense against invading microorganisms by recognizing pathogen-associated molecular patterns (PAMPs). They function as molecular sensors to detect microbial conserved components and trigger protective responses ranging from secretion of cytokines that increase the resistance of infected cells and chemokines that recruit immune cells to cell death that limits microbe spreading.

TLRs are a family of pattern recognition receptors. To date, 11 human TLRs and 13 mouse TLRs have been identified, and each TLR appears to recognize distinct PAMPs

derived from various microorganisms, including bacteria, viruses, protozoa and fungi [2]. TLR1 forms heterodimer with TLR2 (TLR1/2) and recognizes triacyl lipopeptides [65]. TLR2 in concert with TLR1 or TLR6 recognizes a wide variety of PAMPs, including peptidoglycan, lipopeptides and lipoproteins of Gram-positive bacteria, mycoplasma lipopeptides and fungal zymosan [63]. TLR3 recognizes double-stranded RNA [3]. TLR4, together with its extracellular components such as MD-2 and CD14, recognizes lipopolysaccharide (LPS) [25, 53], the endotoxic component of Gram-negative bacteria. TLR5 recognizes protein ligand, bacterial flagellin [19]. TLR6 in association with TLR2 (TLR2/6) recognizes diacyl lipopeptides [64]. TLR7 and TLR8 recognize single-stranded RNA [22, 36], which would be found during viral replication. TLR9 recognizes unmethylated deoxycytidyl-phosphate-deoxyguanosine (CpG) motifs [23] present in bacterial and viral genomes. No ligand has been identified for TLR10 and TLR11.

Despite divergent ligands, most TLRs share a common signaling pathway via the adaptor molecule, myeloid differentiation primary-response protein 88 (MyD88) [1, 32, 62]. Upon stimulation, TLRs recruit MyD88 through their toll/interleukin-1 receptor (TIR) domains. The signal is propagated via IL-1R-associated kinase (IRAK) and tumor necrosis factor (TNF) receptor-associated factor-6 (TRAF6), leading to the activation of NFκB and MAP kinases, and the expression of various inflammatory cytokine genes [1, 32, 62]. In addition to the MyD88-mediated signaling pathway, two TIR-containing adaptor molecules, TIR-domain-containing adaptor inducing IFN-β (TRIF) [68] and TRIF-related adaptor molecule (TRAM) [70], mediate the MyD88-independent signaling pathways leading to the activation of the late phase of NFκB and IFN regulatory factor 3 (IRF-3) and the subsequent production of type I IFN (IFN α/β), IFN-inducible gene products, and an immune regulatory response [1, 69].

TLRs were previously considered to express only in immune cells. The recent studies demonstrate that TLRs are expressed in some tumor cells, and the expression of TLRs in these cells is related to tumorigenesis. Here, we review the differential expression of TLRs in normal and cancerous cells as well as TLR mediated cancer pathogenesis, and discuss the possibility of TLR as a target for tumor therapy.

Expression of TLRs in normal non-transformed cells

TLR was first found expressed as a receptor involved in embryonic development of the fly [5]. It was later demonstrated that Toll deficient flies were highly susceptible to fungal [34] and Gram-positive bacterial infections [35]. The Toll-related proteins were first discovered in mammals in 1997 [38] and the mammalian TLR4 was quickly demonstrated to be responsible for the recognition of LPS and subsequent cellular responses [53].

The expression of TLRs on mature cells has been extensively studied. TLRs are mainly expressed in human immune related cells, such as monocytes, neutrophils, macrophages, dendritic cells (DC), T cells, B cells and NK cells. Differential expression patterns of the TLRs in immune cells were well reviewed [37]. In these cells the engagement of TLRs with their ligands derived from microbes triggers innate immune response to pathogens. More recently, the expression of TLRs on haematopoietic precursor cells has been detected, suggesting a possible role for TLRs in haematopoiesis [42].

Since epithelium is the first line in defense of invasion of microorganisms, TLRs are supposed to express in epithelial cells and may play an essential role in the defense against microbes by recognizing conserved bacterial molecules (Table 1). Indeed, TLR4, TLR5 and TLR9 were expressed on the gastric epithelium of human stomach [57] and TLR3 and TLR5 were constitutively expressed in the ileal mucosa [66]. In the mucosa of active pouchitis, the expression of TLR2 and TLR4 was strongly up-regulated [66]. The colonic epithelium provides an interface between the host and microorganisms colonizing the gastrointestinal tract. It has been reported that TLR2, 3, 4, 5, 7 and 9 are expressed in the healthy human colon [15, 48, 49, 73]. Moreover, TLR2 and TLR4 were demonstrated expressed in a compartmentalized manner in the gut. TLR4 expression was increased in the distal colon, but TLR2 was expressed more strongly in the proximal colon. Both of genes were up-regulated during experiment-induced inflammation [48]. TLR2 and TLR4 were expressed only in crypt epithelial cells, the expression was lost as the cells matured and moved towards the gut lumen. In contrast, TLR3 was only produced in mature epithelial cells [13].

Respiratory epithelial cells are continuously exposed to microbial challenges as a result of breathing. TLR4 are constitutively expressed in distinct human alveolar and bronchial epithelial cells. TLR4 expressed in pulmonary epithelial cells was responsive to LPS [17]. TLR9 is also expressed by respiratory epithelial cell lines and fully differentiated primary epithelial cells. Stimulation of these cells with bacterial DNA or CpG oligodeoxynucleotide resulted in an inflammatory reaction [52].

It was reported that several TLR genes were expressed in some epithelial cell lines derived from human reproductive tract [14, 56]. Constitutive mRNA expression of TLRs 1–6 was observed by RT-PCR in fallopian tubes, uterine endometrium, cervix, and ectocervix [50]. In vivo evidences studied by immunohistochemistry further confirmed that TLR1, 2, 3, 5, and 6 were present in the epithelia of different regions of female reproductive tract. Interestingly,

Table 1 Differential expression patterns of TLRs in epithelia

Tissues	Toll-like receptors	References
Gastric epithelium	TLR4, TLR5, TLR9 (IHC)	[57]
Ileal mucosa	TLR3, TLR5 (IHC)	[66]
Active pouchitis	TLR2, TLR4 (IHC)	[66]
Colonic epithelium	TLR2, TLR3, TLR4, TLR5, TLR7, TLR9 (PCR); TLR2, TLR3, TLR4 (IHC); TLR4, TLR9 (WB)	[15, 48, 49, 73]
Respiratory epithelium	TLR4, TLR9 (PCR); TLR4 (WB); TLR4, TLR9 (FT)	[17, 52]
Fallopian tubes, endometrium, cervix and ectocervix	TLR1, TLR2, TLR3, TLR4, TLR5, TLR6 (PCR)	[50]
Fallopian tubes, endometrium, cervix, ectocervix and vagina	TLR1, TLR2, TLR3, TLR5, TLR6 (IHC)	[13]
Endocervix, endometrium and fallopian tubes	TLR4 (IHC)	[13]
Cervical epithelium	TLR1, TLR2, TLR3, TLR5, TLR6 TLR7, TLR9, TLR10 (PCR); TLR3, TLR9 (FT)	[4]
Keratinocytes	TLR1, TLR2, TLR3, TLR4, TLR5, TLR9 (PCR); TLR2, TLR4 (FT)	[39, 51]

Reverse transcriptase PCR (PCR), Immunohistochemistry *IHC*, Western blotting *WB*, function tested *FT*

TLR2 was expressed highest in fallopian tube and cervical tissues, followed by endometrium and ectocervix. In contrast to TLR2, TLR4 expression declined progressively along the tract, with highest expression in the upper tissues (fallopian tubes and endometrium), and was hardly detectable or absent in ectocervix and vagina [13, 50]. These data suggest that TLRs are differentially expressed in distinct compartments of the female reproductive tract. It is likely that TLR distribution in the female reproductive tract reflects the immunological tolerance to the commensal organisms in lower parts of the tract (vagina, ectocervix and, partially, endocervix) and the intolerance to commensal microbial flora in the upper tract (the uterus and uterine tubes) [13, 50]. It was reported in another study that cervical mucosal epithelial cells express functional TLR3 and TLR9 and response to stimulation of polyinosine-polycytidylic acid [poly(I:C)] and CpG oligodinucleotides, suggesting that these receptors play a role in regulating the proinflammatory cytokine and antiviral environment of the lower female reproductive tract during infection with viral and bacterial pathogens [4].

In addition, human keratinocytes were found to constitutively express TLR1, TLR2, TLR3, TLR4, TLR5, and TLR9 detected by RT-PCR analysis, and the functional expression of TLR2 and TLR4 was also confirmed [39, 51]. Primary astrocytes constitutively express TLR2, TLR4, TLR5, and TLR9. The functional expression of these receptor proteins is further supported by the ability of known ligands for each TLR to induce expression of the proinflammatory cytokine [8]. Furthermore, the constitutive expression of the ten human TLRs was successfully detected in pooled specimens of fetal tissues and single and pooled specimens of various adult tissues by RT-PCR [44].

Expression of TLRs in tumors

Since the immune cells use TLRs to recognize microbial conserved components and then initiate immune and inflammatory responses, TLRs have been previously considered to express only in immune cells. The immunomodulatory properties of TLR agonists have inspired their use as experimental adjuvants for vaccination of cancer patients. However, there is now increasing evidence to suggest that TLR expression is not confined to cells of the immune system. Although there are a limited number of studies on the association between TLR expression and human malignancy, several recent reports on the expression of TLRs and cancers have been published (Table 2).

The relationship between TLR expression on a malignant epithelial tumor and its precursor lesion was first reported [58]. With immunohistochemistry TLR4 and TLR5 were detected to express in gastric epithelium with intestinal metaplasia and dysplasia, and strongly express in tumor cells of gastric carcinoma patients, but not in noninflamed gastric mucosa. The interaction of TLRs expressed in the gastric epithelium with Helicobacter pylori may result in chronic active gastritis that is related to gastric intestinal metaplasia, dysplasia and carcinoma. Thus, TLR expression is likely a dangerous potential since it enables gastric carcinoma cells to interact with H. pylori and induce gastric carcinoma-promoting factors such as IL-8 [58].

Expression or up-regulation of some TLRs has been demonstrated in many other epithelial derived tumors or tumor cell lines. Colon cancer cell lines HT29 and CACO-2 express different levels of TLR1-4 [15]. TLR2 mRNA was detected in colon cancer cell lines DLD and LoVo [71]. TLR2, TLR3, TLR6, and TLR9 were consistently expressed in hepatocellular carcinoma cell Hep G2 [44] and

Table 2 TLR expression in various human tumor cells and tissues

Cells and tissues	Toll-like receptors	References
Gastric carcinoma	TLR4, TLR5, TLR9 (IHC); TLR4, TLR5 (FT)	[58]
Colon cancer	TLR1–4 (PCR); TLR2 (FT)	[15, 71]
Hepatocellular carcinoma	TLR2, TLR3, TLR4, TLR6, TLR9 (PCR)	[44, 71]
Epithelial ovarian cancer	TLR4 (PCR, IHC, WB, FT)	[30]
Cervical squamous cell carcinomas	TLR5, TLR9 (IHC, FT)	[31, 33]
Breast cancer	TLR4, TLR9 (PCR, DNA arrays); TLR9 (IHC, WB, FACS, FT)	[21, 40]
Prostate cancer	TLR9 (IHC, WB, FT)	[29]
Lung cancer	TLR2, TLR3, TLR4, TLR9 (PCR); TLR4 (FACS); TLR9 (IHC, ISH, FT)	[12, 21]
Melanoma	TLR3 (WB); TLR4 (PCR, IHC); TLR3, TLR4 (FT)	[41, 55]
Neuroblastoma	TLR4 (PCR, FACS, FT)	[18]

Reverse transcriptase PCR (PCR), Immunohistochemistry *IHC*, Western blotting *WB*, in situ hybridization *ISH*, flow cytometry *FACS*, function tested *FT*

TLR4 mRNA was detected in PLC/PRF/5 cell [71]. Breast cancer cell responsiveness to LPS suggests that functional TLR4 can be expressed in breast cancer cells [72]. TLR9 protein is also expressed in human breast cancer cells and clinical breast cancer samples [40]. Melanoma cells express TLR3 and TLR4 [41, 55]. TLR4 is expressed in epithelial ovarian cancer cells [30]. Expression of TLR5 and TLR9 is up-regulated in cervical squamous cell carcinomas [31, 33]. The mRNA expression of the ten human TLRs was even detected by RT-PCR in HeLa cells, a cervical cancer cell line [44]. TLR4 is functionally expressed on human lung cancer cell lines [21]. High expression of TLR9 was detected in clinical samples and cell lines of lung cancer as well [12]. In these cells, stimulation of TLR9 with its agonists was shown to result in cytokine production. Sequence variants of TLR4 are associated with prostate cancer risk [9, 74]. Human prostate cancer cell lines and clinical samples exhibit various levels of TLR9 expression [29]. Treatment of TLR9-expressed cells with CpG-oligodeoxynucleotides or bacterial DNA increased their invasion. TLR9-mediated invasion may represent a novel mechanism through which infections promote prostate cancer. In addition, human NB-1 neuroblastoma cells expressed intracellular form of TLR4, but not the cell surface form. Although the cells expressed TLR4 and possessed all the molecules required for LPS response, they did not respond to LPS. It might be responsible for intracellular expression of TLR4 [18].

TLR expression and cancer pathogenesis

The contribution of microbial infection to tumorigenesis is usually ascribed to infection-associated inflammation. Recently, it has been reported that TLRs were expressed by some kinds of tumor cells. However, what is the biological function of TLRs on tumor cells remains to be fully understood. It is therefore mandatory to explore the potential effects of TLR triggering directly on tumor cells. There are now some evidences indicating that expression of TLRs on tumor cells promotes directly or indirectly tumor progression.

The cervical intraepithelial neoplasia (CIN) is a key stage in tumorigenesis of cervical cancers. Expression of TLR5 and TLR9 was undetectable or weak in normal cervical squamous epithelial tissues, but gradually increased in accordance with the histopathologic grade from low-grade cervical CINs, high-grade CINs, and invasive squamous cell carcinomas [31, 33]. The findings suggest that TLR5 and TLR9 may play a significant role in tumor progression of cervical neoplasia and may represent a useful marker for malignant transformation of cervical squamous cells.

TLR4 and TLR9 are functionally expressed on human lung cancer cell lines [12, 21]. TLR4 ligation promotes production of immunosuppressive cytokines TGF-β, VEGF, proangiogenic chemokine IL-8 by human lung cancer cells. In addition, TLR4 ligation induces resistance of human lung cancer cells to TNF-α or TRAIL-induced apoptosis. Therefore, TLR4 expressed on human lung cancer cells may play important roles in promoting immune escape of human lung cancer cells by inducing immunosuppressive cytokines and apoptosis resistance [21]. Treatment of lung cancer cell A549 with TLR9 agonist CpG-oligonucleotides resulted in proinflammatory cytokine production and reduction of spontaneous and TNF-α induced apoptosis, suggesting that the functional expression of TLR9 in human malignant tumors might affect treatment approaches using CpG-oligonucleotides and malignant cells can be regarded as active players in tumor-immunology [12].

Interestingly, Listeria monocytogenes (Lm) survives in the microenvironment of large tumors, resulting in the promotion of tumor growth by activating tumor cell TLR [23]. Lm did not affect the percentage of regulatory T cells or myeloid suppressor cells in the tumor. Through TLR2

signaling, Lm activated MAPK and NFκB in tumor cells, resulting in the increased production of nitric oxide and IL-6 and increased proliferation of tumor cells. All of these effects were abrogated by silencing expression of TLR2. The interaction of H. pylori with tumor cells from gastric carcinoma patients resulted in similar effects. These findings provide a new insight into infection-associated tumorigenesis and illustrate the importance of antibiotic therapy to treat tumors with bacterial infiltration [27]. The infection-induced inflammation due to the activation of tumor cell NFκB is likely to be an important factor favoring tumor progression. However, attention should also be paid to the effects of the pathogens on the tumors because the signaling induced by the interaction between bacteria and tumor cell TLR results in the continuous activation of NFκB and MAPKs in tumor cells and thus drives proliferation directly [27].

On the other hand, TLR3 on some tumor cell induces inhibition and apoptosis of tumor cells. Synthetic dsRNA induces apoptosis of human breast cancer cells in a TLR3-dependent manner [54]. The dsRNA-induced cell death involves the proapoptotic role of IRAK4 and NFκB downstream of TLR3 as well as the activation of the extrinsic caspases [54]. Melanoma cells express TLR3 and TLR4 [41, 55]. Stimulation of melanoma cells with LPS up-regulated the production of IL-8 and cell adhesion. These effects were associated with the constitutive expression of TLR4 mRNA in these cells [41]. In contrast, the engagement of the receptor by TLR3 agonists can directly inhibit cell proliferation and induce tumor cell death when combined to treatment with either type I IFN or protein synthesis inhibitors [55]. These effects were largely dependent on TLR3 shown by RNA interference. TLR3-mediated cell death involves the activation of caspases and engages both extrinsic and intrinsic apoptotic pathways [55]. These evidences suggest that TLR3 agonists represent very promising adjuvants for cancer vaccines not only based on their well-described immunostimulatory properties, but also due to their newly identified cytostatic and cytotoxic effects directly on tumor cells [55]. It may open new clinical prospects for using TLR3 agonists as cytotoxic agents in selected cancers [54].

Although the polymorphism of TLRs does not always affect their expression levels, the increasing evidences link it to the cancer risk. As we mentioned above that TLR4 polymorphism are associated with prostate cancer risk [9, 10, 74]. TLR2 −196 to 174del polymorphism may increase the risk of gastric cancer in the Japanese population [61]. Moreover, polymorphism of TLR4 gene increases risk of gastric carcinoma and its precursors [24]. A heterozygous Thr 135 Ala polymorphism at leucine-rich repeat (LRR) of TLR4 was reported in patients with poorly-differentiated gastric adenocarcinomas. This mutation from threonine to alanine may affect phosphorylation of TLR4 protein and is related to the development of the tumor [45]. The TLR2 −16933T > A variant was associated with an increased risk of follicular lymphoma and a decreased risk of chronic lymphocytic leukaemia. Furthermore, the TLR4 Asp299 Gly variant was positively associated with the risk of mucosa-associated lymphoid tissue lymphoma and Hodgkin's lymphoma [43]. Microsatelite GT polymorphisms of TLR2 gene and Asp299Gly polymorphism of the TLR4 gene is also associated with sporadic colorectal cancer among Croatians [7]. It has been reported that sequences variants of TLR3 and TLR10 may be relevant to Nasopharyngeal carcinoma susceptibility in the Chinese population [20, 75]. Further investigations need to done in order to elucidate the mechanism which TLR polymorphisms are associated with tumors.

TLR as a target for tumor therapy

Microbial components have been used for many years to enhance anti-cancer immune responses. However, the exact mechanism by which these microbial components induce immune responses was not fully elucidated until recently. It is now clear that the anti-cancer effects of microbial components are mediated through TLR signaling [46, 59, 67]. For example, the Bacillus Calmette-Guerin cell wall skeleton (BCGCWS), the active component of the Freund adjuvant, enhances the cytotoxicity of T-cells and macrophages against cancer cells, and induces in vivo anti-tumor effect via TLR2 and TLR4 [67]. The preparation of killed *Streptococcus pyogenes* exhibits anti-cancer effects in a number of malignancies and alipoteichoic acid-related molecule isolated from the bacteria is responsible for most of the anti-cancer effect that is mediated through TLR4 [46].

It was reported that the activation of tumor antigen-specific T-cell immunity involved secretion of the high-mobility-group box 1 (HMGB1) alarmin protein by dying tumor cells and the action of HMGB1 on TLR4 expressed by dendritic cells [6]. During chemotherapy or radiotherapy, DCs require signaling through TLR4 for efficient processing and cross-presentation of antigen from dying tumor cells. Patients with breast cancer who carry a TLR4 loss-of-function allele relapse more quickly after radiotherapy and chemotherapy than those carrying the normal TLR4 allele [6]. In general, TLRs expressed on dendritic cells and TLR signaling induced DC maturation are significant for anti-cancer effect [47, 67]. Since tumor cells prevent dendritic cell maturation induced by TLR ligands, it is possible to develop DC-based cancer immune therapies using TLR ligands as adjuvants for the activation of DC [28].

Previous study indicated that OM-174, a chemically defined TLR2/4 agonist, reduces tumor progression and

prolongs survival in B16 melanoma mice treated with cyclophosphamide [11]. It appears that TLR2/4 agonists induce TNF-α secretion and inducible nitric oxide synthase (iNOS) expression. Nitric oxide is able to induce apoptosis of chemotherapy-resistant tumor cell clones. Moreover, TLR2/4-stimulation activates dendritic cell traffic and its associated tumor-specific, cytotoxic T-cell responses. Therefore, TLR2/4 agonists seem promising molecules to prolong survival in cancer patients who relapse under chemotherapy [16].

As we discussed above, a wide variety of tumor cells express TLRs, direct stimulation of TLRs on tumor cells may lead to production of protein factors and interfere with the fate of tumors. In fact, activation of TLR4 signaling in tumor cells by LPS induces the synthesis of various soluble factors and proteins including IL-6, iNOS, IL-12, B7-H1, and B7-H2, and results in resistance of tumor cells to CTL attack [26]. LPS-stimulated tumor cell supernatants inhibit both T cell proliferation and natural killer cell activity. Blockade of the TLR4 pathway reverses the functions of these cells in vitro, and in vivo, delays tumor growth and thus prolongs the survival of tumor-bearing mice [26]. In epithelial ovarian cancer cells, LPS can promote, directly from the tumor, the production of proinflammatory cytokines, tumor growth and paclitaxel chemoresistance [30]. These findings link TLR4 signaling, inflammation, tumor growth, and chemoresistance in selected cancer cells and indicate that TLR signaling results in a cascade leading to tumor evasion from immune surveillance [26, 30]. These novel functions of TLRs suggest a new class of therapeutic targets for cancer therapy.

Advances in our understanding of the TLRs have led to the identification of several agonists that are suitable for clinical development. For example, TLR agonists may indirectly clear chronic lymphocytic leukemia (CLL) cells by enhancing the activity of natural killer and tumor-reactive T cells, or by altering the tumor microenvironment and inhibiting angiogenesis. However, signaling pathways can be activated directly in CLL cells by TLR7 and TLR9 agonists, leading to the production of cytokines and costimulatory molecules in a manner that is dependent on the underlying cytogenetic abnormalities, but rendering the tumor cells more sensitive to killing by cytotoxic T cells, immunotoxins and some chemotherapeutic drugs [60]. Imidazoquinolines are TLR7 agonists with strong local activity against CLL, and phase I trials are currently ongoing at different centers. The potential importance of these TLR agonists in the treatment of CLL is suggested by their ability to sensitize tumor cells to cytotoxic agents, and their future probably lies in combination with radiotherapies, chemotherapies, monoclonal antibodies and cancer vaccines [60].

Conclusion

There is no doubt that TLRs are expressed on many non-immune cells and tissues, especially epithelium including epithelial derived tumors. Although the TLR profile varies on different tumor cells, functional expression of TLRs has been linked to tumorigenesis. TLR expression may promote malignant transformation of epithelial cells, tumor growth and tumor immune escape, and induce apoptosis resistance and chemoresistance in some tumor cells. TLR agonists are also able to inhibit cell proliferation and induce tumor death in other selected cells. We are convinced that TLR expression on tumor cells would affect the tumor progression and intervention on TLRs will disrupt this process. These make TLR agonists or antagonists the potential drugs for tumor therapy. However, most of studies so far are focused on the tumor cell lines. In order to elucidate the functional association of TLR with tumor further investigation of the TLR expression profile in different types of tumors need to be done. Most importantly, detail mechanism and regulation of TLR functions in tumor pathogenesis are still under studying. What are the exact roles played by microbial components and infections on the tumorigenesis? Interestingly, most tumors express more than one kind of TLRs. How each of these TLRs functions specifically? Although we have many questions to be addressed, the tumor cells do express TLRs and the current evidences indicate that the TLRs are functionally associated with tumor progression. TLRs would be promising targets for tumor therapy.

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